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Bioinformatic evidence of spike-olfactory receptor mimicry: a potential mechanism for anosmia after SARS-CoV-2 infection and vaccination

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Abstract

Anosmia is one of the most common neurological symptoms to occur following infection with SARS-CoV-2, whilst olfactory disorders are rare following vaccination. The immune-mediated response against the olfactory structures could have broad implications for the proper functioning of the central nervous system, as the sense of smell is not only important for the perception of odors but is also closely interconnected with the gustatory, limbic and cognitive circuits. Molecular mimicry between viral and host proteins is one of the plausible mechanisms underlying these effects. In light of this, we carried out a systematic bioinformatic analysis to identify potential linear peptide matches between the human olfactory receptor proteome and SARS-CoV-2 proteins, focusing on the spike glycoprotein. We found multiple peptide matches between olfactory receptors and SARS-CoV-2 proteins, but only OR5H14 shared an identical hexapeptide (ISVTTE) with the

spike glycoprotein, suggesting a possible mechanism underlying the rare spike-mediated post-vaccination olfactory dysfunction. This also explains why, by contrast, greater viral exposure during infection leads to a higher prevalence of anosmia. Furthermore, the shared amino acid sequence segment demonstrated antigenic-immunogenic potential. These findings support a potential role for molecular mimicry between the spike protein and OR5H14 in post-vaccination anosmia, with implications for the sensory and cognitive pathways of the central nervous system, laying the foundations for future immunological studies.

Introduction

Neurological symptoms associated with SARS-CoV-2 infections include anosmia and hyposmia, which have an incidence rate from 30% up to more than 60%.¹⁻³ The pathways responsible for development of these symptoms can be either due to the influence of the virus on local inflammatory response and neuroepithelial homeostasis, but recent studies have focused on the contribution of immune-mediated pathways, especially in long or atypical cases of coronavirus infection.^{4,5} In turn, olfactory symptoms due to coronavirus vaccination are extremely rare, especially for mRNA vaccines like BNT162b2.^{6,7} To date, no definitive causal link has been established between vaccination and olfactory disorders. However, the onset of anosmia following a natural infection or, more rarely, vaccination, raises a question: could these phenomena be caused by a common immunological mechanism in a small subgroup of predisposed individuals?

The answer to this question brings us back to the concept of molecular mimicry, which is defined as the sharing of antigenic determinants between microbial proteins and host proteins, and represents a well-established mechanism in the pathogenesis of autoimmune and immune-mediated diseases.^{8,9}

In the context of COVID-19, several studies, including those carried out by our group, have hypothesized that antigenic overlap between SARS-CoV-2 proteins and human proteins may contribute to the multi-organ damage observed in patients and to post-infectious sequelae.¹⁰⁻¹² In particular, we had previously hypothesized that molecular mimicry might be involved in damage to the olfactory mucosa during SARS-CoV-2 infection, potentially contributing to anosmia and other neurovegetative symptoms.^{11,12}

A characteristic of mRNA vaccines offers a unique opportunity to distinguish between immune responses linked to specific proteins, such as the SARS-CoV-2 spike (S) glycoprotein, and those

associated with the virus's broader antigenic repertoire during natural infection.^{13,14} Based on these principles, we aimed to explore the possible involvement of molecular mimicry as one potential mechanism responsible for the olfactory dysfunction seen in relation to SARS-CoV-2. For this purpose, we carried out a detailed bioinformatics analysis between the proteome of the human olfactory receptors and the proteome of SARS-CoV-2, especially focusing on the spike protein. This was done to establish the common epitopes that may be involved in biological cross-reactivity in terms of immunology and thus cause olfactory dysfunction in SARS-CoV-2 infection or rarely post-vaccination.

Materials and Methods

Protein sequence datasets

From the UniProt database, a comprehensive dataset of human olfactory receptor proteins was obtained, as already described.⁸ In particular, we focused on annotated olfactory receptors expressed in the olfactory epithelium. Furthermore, reference sequences from National Center for Biotechnology Information (NCBI) and UniProt were used to determine the complete proteome of SARS-CoV-2, including both structural and non-structural proteins.

Bioinformatic epitope matching

The sliding-window method was applied to detect similar linear amino acid patterns among the analyzed protein sequences. Then, peptides containing more than six amino acids with 100% sequence identity were considered further for their identification within both human olfactory receptors and SARS-CoV-2 proteins. This criterion was selected based on our earlier findings that short, identical peptide sequences could activate T cell-mediated immune response and, under certain conditions, cross-reactivity of antibodies.⁸ Particular attention was paid to peptide matches involving the SARS-CoV-2 spike glycoprotein, in order to study the effect of the sole viral protein expressed following the administration of mRNA vaccines. Further analyses were performed using the Immune Epitope Database and analysis re-source (IEDB, <https://www.iedb.org/>), a database of experimentally validated epitopes and a tool to predict T cell and B cell epitopes. We used the BebiPred 2.0¹⁵ and the Kolaskar and Tongaonkar Antigenicity scale,¹⁶ both algorithms embedded in the B cell prediction analysis tool available in IEDB.¹⁷ For CD4 T and CD8 T **cell epitope prediction, we applied previously described algorithms developed to predict dominant** Human Leukocyte Antigen (HLA) class I and dominant HLA class II epitopes.^{18,19}

Analytical framework

In the current study, a computational methodology that had already been designed and optimized by our research team for the examination of a possible molecular mimicry of SARS-CoV-2 protein sequences, human molecular chaperones and endothelial antigens in order to make up hypothesis that can be tested experimentally concerning the role of immunological mechanism in the tissue damage caused by COVID-19 disease was used. The computational methodology was adapted here to be applied to the case of human olfactory receptor sequences.

Results

Bioinformatic analysis identified numerous short peptide matches between human olfactory receptors and the SARS-CoV-2 proteome (results shown in Supplementary Table 1). However, most of these matches concerned viral proteins different from the spike protein, including the replicase polyprotein 1ab and accessory proteins, and are therefore potentially relevant to the effects following natural infection with the virus but not to those following mRNA vaccination.

In particular, it was found that only one human olfactory receptor, namely OR5H14 (UniProt ID: A6NHG9), shares an identical peptide sequence with the SARS-CoV-2 spike glycoprotein. Specifically, it is the hexapeptide sequence ISVTTE, located at positions 106–111 of OR5H14, which is identical to the sequence found at positions 720-725 of the spike protein. This represents the only spike-related match identified among all analyzed olfactory receptors. Interestingly, all the shared peptide between OR5H14 and spike protein are part of an immunogenic epitope predicted using IEDB for CD4 T Lymphocytes (Table 1).

Discussion

Our bioinformatic analysis identified several human olfactory receptor proteins sharing identical linear peptide sequences with different SARS-CoV-2 proteins; notably, however, only one receptor (OR5H14) shared an epitope with the spike glycoprotein, the sole viral antigen expressed following mRNA vaccination. Moreover, the results obtained by the bioinformatics prediction tool for immunogenic epitopes showed that the shared peptide have a high likelihood of being recognized by the human immune system, triggering an autoimmune reaction. This finding offers a biologically plausible explanation for the substantial difference in the frequency of olfactory dysfunction seen after natural SARS-CoV-2 infection compared with the much rarer cases reported following mRNA vaccination.

Overall, during natural infection, the host's immune system is exposed to the entire viral proteome, and this can potentially give rise to multiple occurrences of molecular mimicry which, in this specific case, increase the probability of immune-mediated damage to the olfactory structures. By

contrast, as shown in Figure 1, vaccination limits antigenic exposure to the spike protein alone, thereby significantly reducing the number of potential cross-reactive targets within the olfactory system.

Human olfactory receptors constitute a large family of class A (rhodopsin-like) G Protein-Coupled Receptors (GPCRs) expressed as seven-transmembrane, multi-pass membrane proteins in olfactory sensory neurons of the nasal epithelium.²⁰ The location of the olfactory receptors is mainly on the cilia and in the synaptic compartments of the olfactory neurons. Therefore, odorant molecules interact with these receptors by coupling with G protein $G\alpha_{olf}$ specifically expressed by the olfactory neurons to cause neural activation. This process forms a basis for the formation of neural impulses responsible for odor perception. Functionally, olfactory receptors participate in the first step of sensory transduction before further cortical processing linked to other systems of perception and cognition.^{21,22} In this connection, possible immune destruction of the mentioned above membrane receptors or of the olfactory neurons themselves might affect the process of signal transmission at the initial step explaining such conditions as anosmia or hyposmia.

As olfactory stimuli significantly affect the taste perception as well as limbic processes of emotion, memory and decision making,²³⁻²⁶ it can be concluded that impaired function of the olfactory system may considerably affect the quality of life of the individual and, even when transient, should not be considered a minor adverse event. Concerning the transient nature of the observed phenomenon, additional evidence that makes the reversible immune-mediated mechanism plausible is the known regenerative ability of olfactory sensory neurons, which, in contrast to other neurons in an adult central nervous system, are constantly being renewed, making it possible to replace damaged neurons under normal conditions.²⁷ It is reasonable to suggest that in case the immune reaction elicited by molecular mimicry is either self-limiting or temporary, then regeneration of olfactory neurons would make it possible to restore their function. This hypothesis corresponds to clinical observations demonstrating spontaneous or gradual restoration of olfactory function in many patients suffering from olfactory dysfunction not only after coronavirus infection but also, in rare cases, after vaccination.^{2,5-7} Finally, these observations are consistent with the concept of an immunological scheme wherein vaccination, due to the immunization of the host immune system against one viral protein, may interfere with the surpassing of an “infective threshold,” characterized by the presence of high viral titers and extensive tissue tropism observed during natural infection, as previously proposed.²⁸ In particular, by preventing viral infection and thus the exposure of the antigen systemically, vaccination may decrease the chance of conversion of molecular mimicry mechanisms into autoimmune disease. In light of this hypothesis, the rare occurrence of olfactory disorders after vaccination may consist of a few isolated cases wherein the

anti-spike immune response would cross-react with structurally related host proteins, such as OR5H14, without compromising the beneficial effect of the vaccine itself. In conclusion, this theory might lead to some testable hypotheses concerning the identification of spike-reactive autoantibodies or T cells against olfactory receptors in the affected subjects.

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Table 1. Shared peptide sequence between human olfactory receptor OR5H14 and the SARS-CoV-2 spike glycoprotein. OR5H14 was the only olfactory receptor identified to share an identical hexapeptide (ISVTTE) with the SARS-CoV-2 spike protein. The table also reports Immune Epitope Database (IEDB)-derived predictions for the corresponding putative immunogenic epitope.

Shared peptide (≥ 6 amino acids)	Human protein (Uniprot ID)	SARS-CoV-2 protein (Uniprot ID)	Putative epitope/IEDB prediction
ISVTTE	Olfactory receptor OR5H14 (A6NHG9)	Spike glycoprotein (P0DTC2)	720-725 AIPTNFTISVTTEIL/ CD4 T Lymphocytes

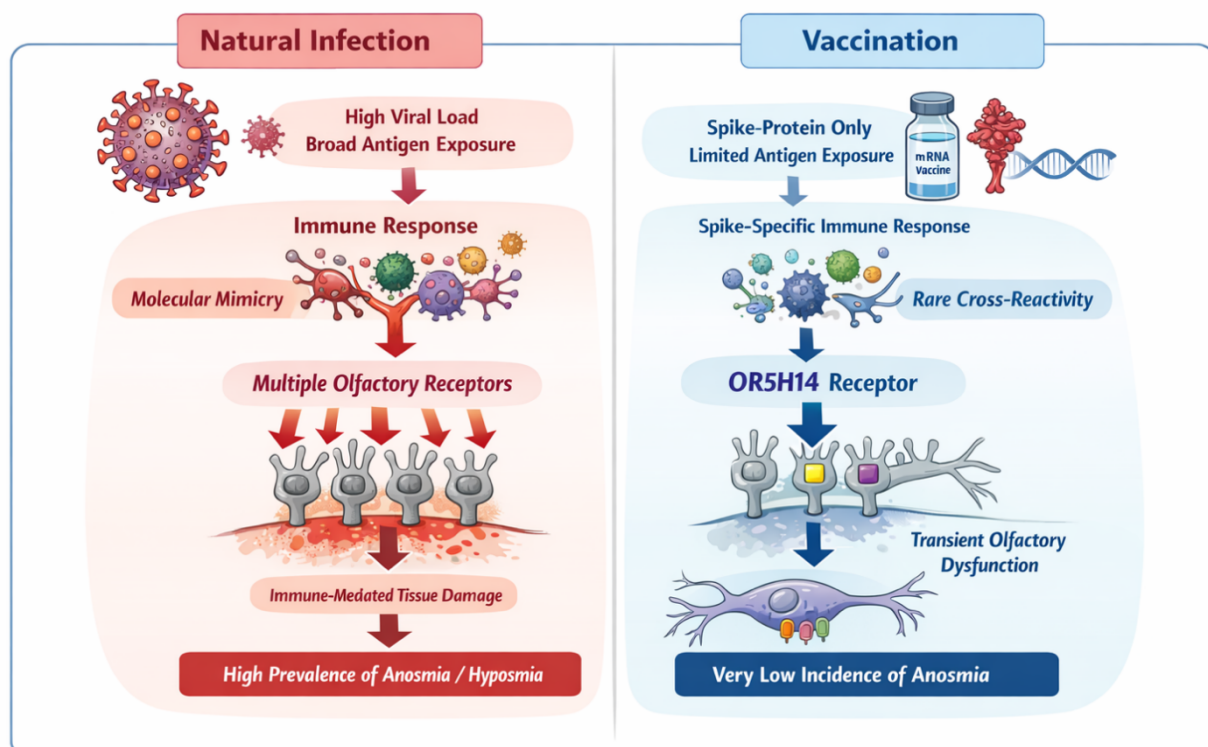


Figure 1. Differential immune outcomes in olfactory dysfunction following SARS-CoV-2 infection versus mRNA vaccination.

Conceptual model illustrating differential immune outcomes following SARS-CoV-2 infection versus vaccination. Natural infection, characterized by high viral load and broad antigen exposure, may surpass an infective threshold favoring immune-mediated tissue damage, including the olfactory mucosa. Vaccination induces a controlled spike-specific immune response that limits viral replication and dissemination, thereby reducing the likelihood of clinically overt autoimmunity. In rare, predisposed individuals, spike-related molecular mimicry may transiently impair olfactory function (e.g., OR5H14). Image conceived by the authors and generated with the assistance of artificial intelligence (ChatGPT).

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Online supplementary materials

Table 1. The table lists human olfactory receptor peptides that show matches with SARS-CoV-2 proteins. Matches were identified through local alignments between olfactory receptor peptides and viral proteins and may highlight regions of potential structural or functional relevance.