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Loss of smell in COVID-19: reasons for variable recovery patterns from anosmia

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To the Editor,

Anosmia, which coupled with altered or loss of taste, during the current pandemic in individuals has heralded the onset of coronavirus disease 2019 (COVID-19). The recovery from the anosmia has been seen to vary among individuals, which in some cases has been seen to take a protracted course, the causes of which is unknown. Direct damages to olfactory ensheathing cells (OECs) and extensive inflammation of the olfactory mucosa (OM) has been implicated as the cause of anosmia in patients with long-COVID. Here I debate the possible mechanisms underlying the variable recovery from anosmia in COVID-19 and reasons why it continues in some patients with long-COVID?

The mammalian olfactory system is unique in that it can constantly regenerate the olfactory receptor cell neurons damaged by environmental olfactory toxins. The olfactory mucosa occupies the upper deeper part of the nasal cavity and the adjoining parts of the nasal septum. A complex network of non-neuronal cells and neural tissues constitute the olfactory mucosa in humans (Glezer and Malnic, 2019) (**Figure 1A1**), The axons of olfactory nerve fibers arising from the receptor cells (neurons) project uninterrupted to the neurons in the olfactory bulb (**Figure 1B**). In the olfactory bulb, they synapse with the antenna-shaped dendrites of the large mitral cells, each mitral cell gives origin to an elongated axon, many of which enter into the formation of the olfactory tract, a band extending from the bulb over the basal surface of the forebrain (**Figure 1A1**). The olfactory tract distributes its fibers mainly to the cortex of the pyriform lobe. A smaller number of fibers of the olfactory tract ends in the olfactory tubercle and the medial part of the amygdaloid complex. Projections from the pyriform cortex and other forebrain regions, via the thalamus, provide olfactory information to several additional regions of the cerebral cortex. The further processing of smell initiates appropriate motor, visceral, and emotional reactions to olfactory stimuli.

In the olfactory mucosa, diverse cell types are present in two layers: the olfactory epithelium and lamina propria (**Figure 1B1**). The olfactory epithelium includes olfactory receptor neurons, globose and horizontal basal cells (BCs) (Glezer and Malnic, 2019) (neural stem cells) (**Figure 1B1**), sustentacular cells (non-neuronal supporting cells), and Bowman's gland and duct cells. The lamina propria includes olfactory nerve fibroblasts, mesenchymal stem cells, and OECs (Sun et al., 2019) (**Figure 1B1**). The latter surrounds the axonal projection of receptor cell neurons to the olfactory bulb while the BCs within the olfactory epithelium are known to replenish the neurons within the olfactory epithelium (Glezer and Malnic, 2019). OECs support neural regeneration by promoting cell-cell interaction. They have been found to create an environment that is favorable for axon growth and restoration (Glezer and Malnic, 2019; Sun et al., 2019) as well as secreting extracellular matrix molecules, which provide a substrate for newly generated axons.

Though the region from where the samples are obtained to test the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the nasal cavity is distal to the olfactory mucosa, the SARS-CoV-2 appears to seed deeper into the superiorly located olfactory mucosa as reported in recent studies (Bulfamante et al., 2020). Inflammation of the olfactory mucosa by SARS-CoV-2 is believed to be the basis of anosmia in COVID-19, and in mice damage to the olfactory sustentacular and olfactory stem cells by SARS-CoV-2 is thought to be the cause of anosmia. Previously, autopsy findings of fresh specimen in COVID-19, the SARS-CoV-2 has been found to cause severe damage to the olfactory nerve fibers and in regions as deeper as the olfactory bulb and the inferior surface of frontal lobe of the brain (Bulfamante et al., 2020) related to the olfactory bulb.

For patients tissues suffering loss of smell in COVID-19, apprehensions persist regarding the duration for which the anosmia would continue, also the clinicians cannot provide a definitive timeline for the restoration of olfactory function back to normal. The answer to recovery from anosmia is complex, as has been observed with the outcomes of anosmia in COVID-19. Some of the patients report recovery over weeks while others continue to suffer anosmia with or without loss or altered taste for months after its onset (Sun et al., 2020). The variable viral load caused by SARS-CoV-2 and the outcomes of the inflammation in nasal mucosa could the reasons behind the differences seen in the recovery from anosmia seen in COVID-19, but the damage to peculiar cells like BCs and OECs in the olfactory mucosa with a loss of the regenerative capability of the olfactory receptor neurons and axonal extensions (**Figure 1C1** and **C2**) appears to be the reason for the cases of persistent anosmia in COVID-19. Direct invasion of the BCs, OEC, and the olfactory mucosal damage during the reactive inflammatory processes may differ from patient to patient due to the variation in the viral loads of SARS-CoV-2 in patients with COVID-19. In cases of the patients with COVID-19 with anosmia that is seen to resolve within weeks, a replacement of the damaged cells by BCs and OEC could be in effect. Limited inflammation or low viral loads in the olfactory mucosa without the loss of a large number of BCs and OEC could allow partial or complete restoration of the sense of smell that has been seen to revert within weeks in COVID-19. The fact that many patients who enter into a protracted phase of long COVID-syndrome and continue to suffer anosmia and hypogeusia hint towards the possibilities of, a) inadequate eradication of SARS-CoV-2 from the olfactory mucosa, b) permanent damages to the OEC and BCs or, c) ongoing sub-acute or chronic inflammation in the olfactory mucosa. An important consideration in the chronic COVID syndrome seen in long-haulers is impairments with the cortical processing of olfactory information as many of the affected individuals suffer cognitive disorders of complex pathogenesis, which also may be the cause of the altered smell reported in these patients.

After reports of the significance of the anosmia and hypogeusia in COVID-19 and the neuroinvasive potential of SARS-CoV-2 in early pandemic (Baig et al., 2020), the research on the anosmia and hypogeusia has gained momentum but finding an explanation for the reasons

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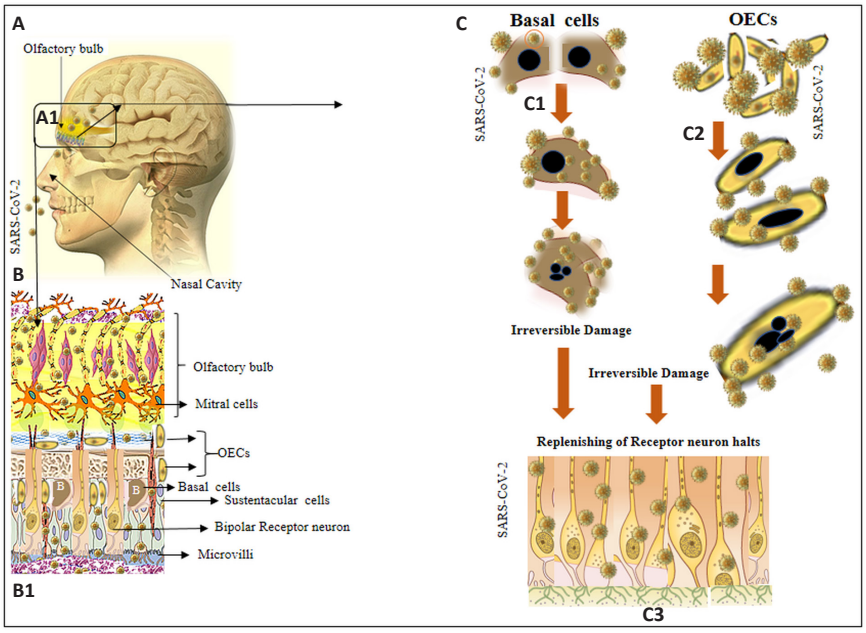

Figure 1 | **The human olfactory pathway and SARS-CoV-2 infection.**
(A–A1) Location of olfactory mucosa and olfactory bulb. (B) Magnified boxed zone in A1 showing the relationship between the (B1) olfactory mucosa, containing the olfactory receptor neurons, basal cells, and OECs with supporting cells. The basal cells replenish the receptor neurons while OECs enable axonal regeneration by providing favorable growth factors and the environment needed for neuronal regeneration. (C) Damage of the basal cells and OECs (C1–C2) by SARS-CoV-2 (C3) can result in the persistence of anosmia in COVID-19. OECs: Olfactory ensheathing cells; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

for variable recovery from these signs and symptoms of loss of smell and taste in patients in COVID-19 needs to be investigated in-depth. A non-invasive way to gauge the density and population of BCs and OECs in patients recovering from COVID-19 can provide a useful guide towards recovery from anosmia as patients would be very much reluctant to opt for invasive methods to determine the chances of recovery from anosmia. As smell is a very pivotal human sense that is essentially needed in day-to-day human physiological functions, nasal transplantation of BCs and OECs or treatment with nerve growth factors could be considered in COVID-19 if anosmia becomes permanent and the smell does not get restored for years after COVID-19.

The author declares no conflicts of interest.

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