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Olfactory Epithelium: Cells, Clinical Disorders, and Insights from an Adult Stem Cell Niche

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Disorders causing a loss of the sense of smell remain a therapeutic challenge. Basic research has, however, greatly expanded our knowledge of the organization and function of the olfactory system. This review describes advances in our understanding of the cellular components of the peripheral olfactory system, specifically the olfactory epithelium in the nose. The article discusses recent findings regarding the mechanisms involved in regeneration and cellular renewal from basal stem cells in the adult olfactory epithelium, considering the strategies involved in embryonic olfactory development and insights from research on other stem cell niches. In the context of clinical conditions causing anosmia, the current view of adult olfactory neurogenesis, tissue homeostasis, and failures in these processes is considered, along with current and future treatment strategies.

Key Words: Olfaction, stem cells, anosmia, regeneration.
Level of Evidence: NA

INTRODUCTION

The human olfactory system is a highly sensitive detector of volatile chemicals. An intact olfactory system can identify minute concentrations of odorants and discriminate among highly similar chemical structures, enabling us to perceive a vast number of unique odors.[1] Chemosensation in many mammals is critical for survival: it is required for the avoidance of predators, the identification of food, and identification or selection of mating partners. While human behavior may rely less on chemical senses, human olfaction is of great importance in safety, to warn of dangers such as smoke, noxious fumes, or spoiled food; in proper nutritional intake, as many of the pleasurable qualities of flavor involve retronasal olfaction; and in daily social interactions. Many disease processes can, however, impair olfaction, including genetic disorders, rhinosinusitis, concussion, post-viral olfactory disorder, or presbyosmia (age-related olfactory decline). While some processes are amenable to current treatments[2–5], ongoing research will be necessary to bring novel therapies to physicians caring for olfactory disorders. Recent advances have provided tremendous insight into the organization and function of the peripheral olfactory system, as well as the production of new olfactory cells from adult stem cells residing in the olfactory neuroepithelium of the nose. Here, olfactory function, dysfunction, and the reparative properties of the olfactory system are reviewed, with a focus on potential for new treatment approaches. The majority of information comes from animal models, unless specifically indicated that studies involved human tissue.

Anatomy and Organization of the Peripheral Olfactory System

The olfactory epithelium (OE) in the nose is the peripheral organ for the sense of smell. A large range of organic compounds, generally having a hydrophobic region and a molecular weight under 300, can be perceived as odors by humans.[6] In the initial step in olfaction, inspired odor molecules interact with olfactory sensory neurons (OSNs) in the nasal cavity, situated in the lining the olfactory cleft (Fig. 1A,B). The mucosa of olfactory cleft contains the OE. A true neuroepithelium, rather than respiratory epithelium, the OE is situated along the superior medial vertical lamellae of the superior turbinates, a similar small portion of the middle turbinates, and the corresponding nasal septum.[7] In general terms, a sensory system involves the conduction of a stimulus to receptor structures, a transduction apparatus to convert the stimulus into a neural signal, and a sensory relay to a second order processor. The conduction system in the nose requires that airflow can successfully deliver inspired odorants to the olfactory cleft, without obstructing disease such as edema or polyps. In the OE, the OSN is the critically important cell and functions as the receptor, transduction and relay apparatus (Fig. 1).

Odorant-binding specificity occurs due to odorant receptor (OR) proteins, which are members of the superfamily of seven-transmembrane domain G-protein coupled receptors, expressed by OSNs. Of the estimated several million neurons lining the olfactory cleft, there exist approximately 350 functionally distinct "types" of OSNs in humans, scattered in broad zones, with each "type" of neuron defined by its expression of one specific

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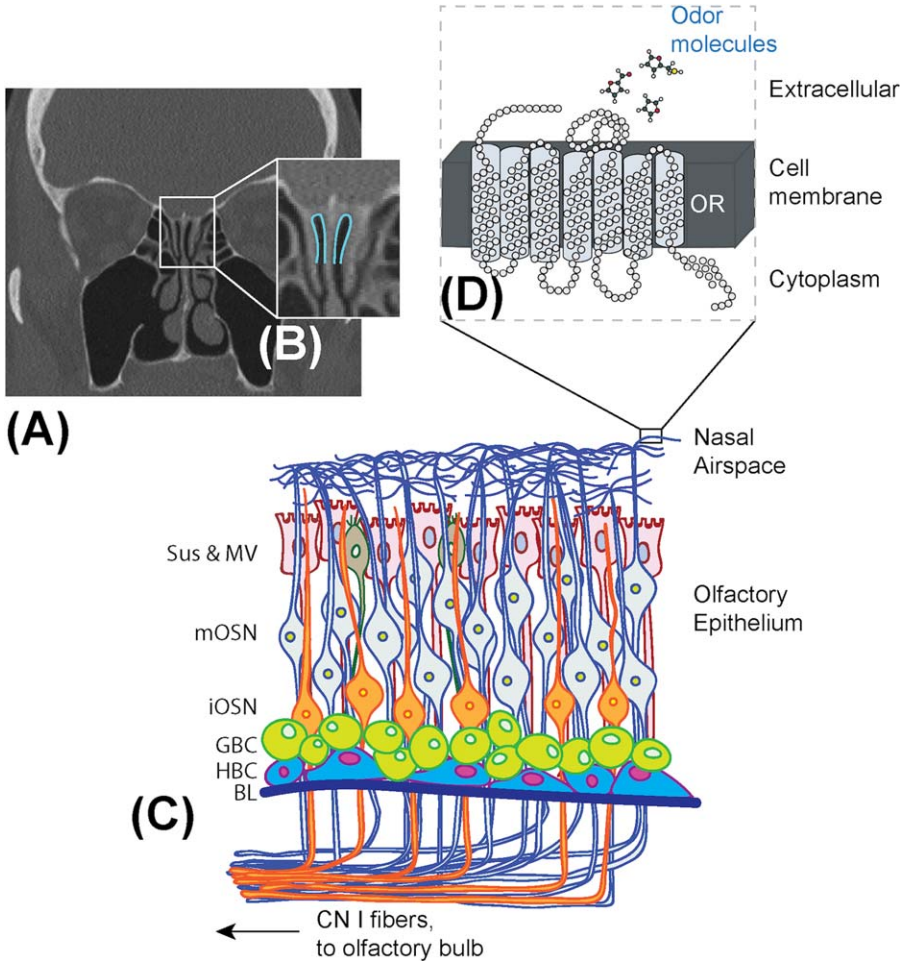

Fig. 1. Overview of the peripheral olfactory system. Within the nasal cavity, the OE is the peripheral organ for the sense of smell. **(A)** While respiratory epithelium lines the majority of the nasal cavity, OE lines the region of the olfactory cleft. On a coronal CT image through the nasal region, the olfactory cleft **(box)** is seen in the superior medial area. **(B)** On closer view of the olfactory cleft, the area lined by OE **(blue)** is indicated. The cribriform plate bone separates nasal cavity from cranial cavity, with the olfactory bulbs and crista galli seen superior to the olfactory cleft. OE lines the medial superior vertical lamellae of the superior turbinates and the corresponding superior septum. However, there is considerable variability among individuals, with biopsy samples often showing patches of respiratory epithelium from superior olfactory cleft. **(C)** The composition of the OE is shown schematically. OE is a pseudostratified neuroepithelium, housing the cell bodies of mature olfactory sensory neurons **(mOSN),** as well as immature neurons **(iOSN)** produced from basal stem cells. Two populations of stem and progenitor cells, the globose basal cells **(GBC)** and the horizontal basal cells **(HBC)**, support life long self-renewal of the OE, replacing neurons as needed. Glia-like sustentacular **(Sus)** and sensory microvillar **(MV)** cells are situated apically. Axons from OSNs exit the base of the OE and their fascicles project as the first cranial nerve **(CN I)** through the cribriform plate to synapse in the olfactory bulbs. At the nasal airspace, OSNs extend a mat of immobile cilia **(blue)** from their dendritic knobs. **(D)** The cilia are the site of odor transduction. Inspired odor molecules are recognized by odor receptors **(OR)** expressed at the neuronal cilia membranes. ORs are seven-transmembrane domain G-protein coupled receptors. OR activation leads to OSN depolarization and signaling to specific olfactory bulb glomeruli. BL indicates basal lamina.

OR gene from a repertoire of 350 possible genes.[8–10] OR proteins may be narrowly or broadly tuned; however, most ORs can be activated by a range of compounds that share a common structural group or backbone.

The bipolar-shaped neurons extend a dendrite to the airspace at the epithelial surface, and extend an axon through the base of the epithelium to join other axons forming the first cranial nerve (CN I). The dendrites end in a dendritic knob apically, which extends multiple immotile cilia in the mucus layer, greatly extending membrane surface area for the molecular recognition of odor molecules by ORs at neuronal cilia membranes[11,12] (Fig. 1C, D). The primary projection of OSN axons from the nose to the glomerular layer of the olfactory bulb of the brain establishes a spatial odor map. Because axons from OSNs expressing a given OR converge only to specific glomeruli in the bulb, where they synapse with mitral or tufted cells, the odorant-induced glomerulus activation pattern represents the initial coding of odor.[13] The human olfactory bulb bears the same general laminar organization seen in commonly studied animal models, however it does appear to differ in some respects from rodents.[14] In humans, the olfactory bulb has, on average, over 5000 glomeruli, such that there is a high ratio of convergence of glomeruli/OSNs innervating them, indicating that complex initial odor coding occurs at this tissue.[14] Higher center

TABLE I.
Selected Causes of Olfactory Dysfunction.

Category	Condition	Details/Mechanisms
Genetic	Kallmann Syndrome	Defects in projection and migration from olfactory placode may lead to failure in olfactory bulb development.
	Ciliopathies	Olfactory neurons in the OE express odorant receptors on the membranes of immotile cilia. In disorders in which cilia are malformed or absent, odor transduction cannot occur. Examples include Bardet-Biedel, Meckel-Gruber and Joubert syndromes.
Inflammatory	Chronic rhinosinusitis	Edema with or without polyps may cause obstruction of the olfactory cleft. Also, inflammatory cytokines may directly impair OSN function or survival. Cytokines may alter the reparative response of basal cells.
	Rhinitis/allergy	Obstruction from allergic edema may cause conductive hyposmia.
Aging	Presbyosmia	Biopsy evidence suggests that cumulative damage or "wear and tear" may lead to neurogenic exhaustion in the OE, or a failure in tissue maintenance. It is also possible that central degenerative changes occur.
	Neurodegenerative disease (Alzheimer's, Parkinson's)	Hyposmia/anosmia often precedes other general symptoms; evidence suggests olfactory bulb neurons dependent upon renewal via the rostral migratory stream may be involved.
Head trauma	Concussion, Traumatic brain injury	Blunt head injury, especially to the occiput, causes a coup-contrecoup injury with shearing of the delicate olfactory nerves projecting through the cribriform. Damage to olfactory bulbs/cortex may also occur. A lack of recovery suggests a failure of OSNs to successfully reinnervate the olfactory bulbs.
Post-viral olfactory disorder	Anosmia occurs following resolution of upper respiratory infection	Etiology unclear. Recovery can occur over several months, although approximately 1/3 of patients do not recover. Biopsies demonstrate peripheral damage to the OE, with a failure in normal OE reconstitution from basal stem cells.

processing, involving areas such as the entorhinal and pyriform cortex, is beyond the scope of this review. Since odor conduction, recognition, transduction and initial coding all occur in the periphery, it is evident that the maintenance of a population of OSNs in the nose, and their projection to synapse with their targets in the olfactory bulbs, is necessary for an intact olfactory sensory system.

A Vulnerable Sensory System

Due to their position in the nose in contact with the inspired air, the OSNs are considered to be highly vulnerable to a variety of insults that may lead to their degeneration and loss. How is a population of OSNs maintained throughout life? Pathogens such as virus or bacteria, inflammatory cytokines in the mucus such as products of eosinophil granules, inspired toxins or chemicals, or blunt head injuries causing mechanical shearing of their delicate axon fascicles projecting through the cribriform plate, can all lead to OSN death[15–17] (Table I). Indeed, classical mitotic labeling data from animal studies suggest that, on average, OSNs may only survive on the order of months.[18] More recent findings indicate that OSNs situated more dorsomedially likely survive longer than the ventrolateral populations, perhaps due to differences in the expression of certain detoxification enzymes.[19] Nonetheless, it is evident that over many decades of life, humans must maintain a capacity for the replacement of OSNs to sustain an intact olfactory system. An age-related decline in olfaction, termed presbyosmia, is well described, and may be reflective of cumulative damage that has exhausted normal repair mechanisms.[20–22]

Tissue Homeostasis: Basal Stem Cells

The replacement of OSNs is accomplished normally by the presence of populations of basal stem and progenitor cells in the OE.[23–29] The basal germinal zone of the OE is an active neurogenic niche, capable of producing new neurons from bona fide neural stem cells (Fig. 2). The robust capacity for ongoing neurogenesis in the OE contrasts with most other regions of the adult nervous system. In mouse or rat, models of experimentally induced olfactory injury have been used to study the damage-induced proliferation and differentiation of basal cells in the OE.[24,26,30–32] Using an experimental approach termed genetic fate mapping, multiple categories of distinct OE stem or progenitor cell populations have been defined, along with the specific types of progeny cells that they can produce.[28,29,33,34] In this technique, mice are engineered so that cells expressing a gene of interest will also produce a heritable reporter protein that can be visualized in tissue sections. Often, activation of the labeling mechanism is designed to be manipulated under pharmacologic temporal control.[35] Daughter cells, and subsequent generations of progeny cells, produced from these founder cells will also be identifiable by expression of the reporter (e.g. a fluorescent protein). Such lineage tracing studies have defined the lineages of two distinct categories of OE stem cells: the reserve horizontal basal cells, which generally remain mitotically quiescent unless activated by injury, and the globose basal cells, which are a heterogeneous population of both reserve and active progenitors. Thus, the OE is a self-renewing tissue, and epithelial homeostasis results from the replacement of senescent cells from basal progenitors.

In many respects, the adult OE appears to retain certain embryonic properties, in terms of the biochemical

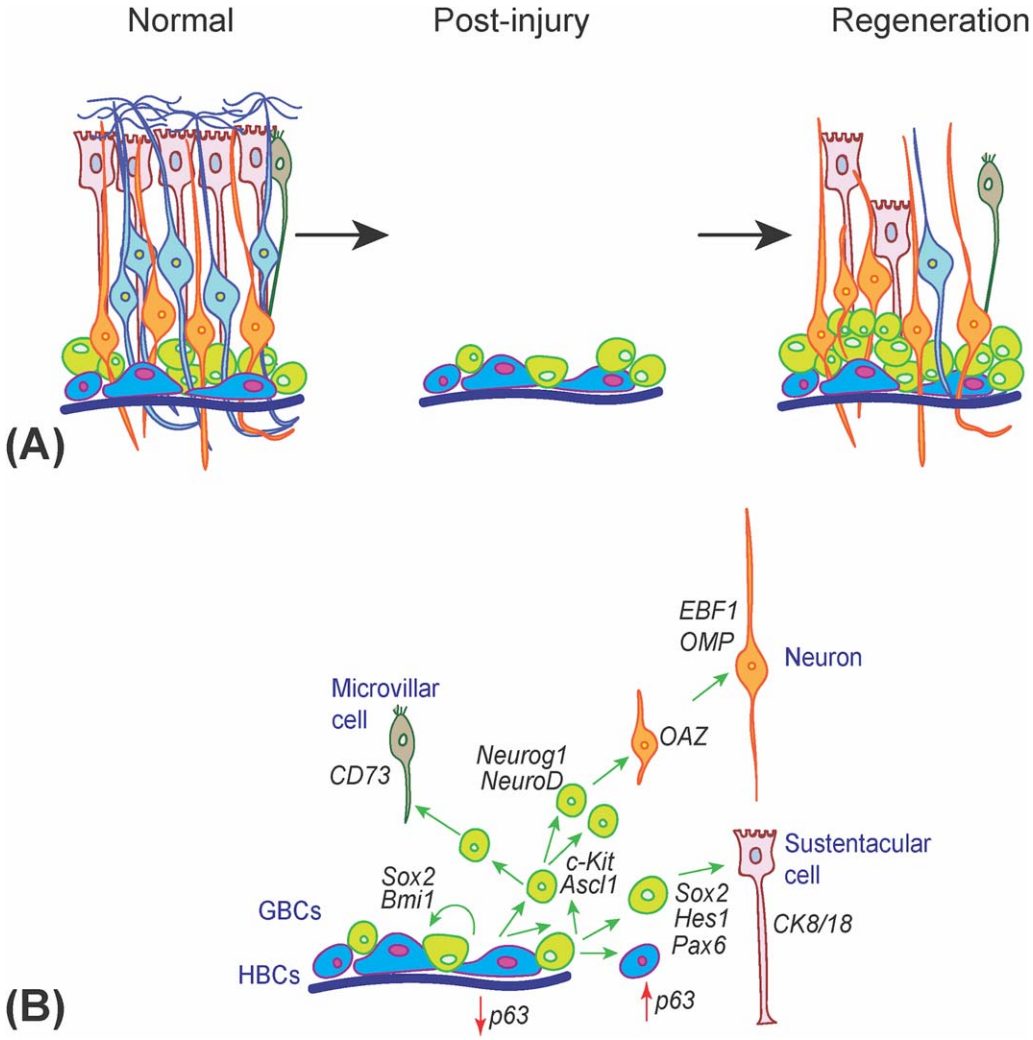

Fig. 2. Adult stem cells and tissue homeostasis in the olfactory epithelium (OE). The population of olfactory sensory neurons (OSNs) are inherently vulnerable to damage and death, positioned in contact with the nasal airspace. However, mammals have retained an ability to replenish OSNs, and the other cells of the OE, from populations of basal neural stem cells, the horizontal basal cells (HBCs) and globose basal cells (GBCs) described in **Fig. 1**. **(A)** A schematic depiction of injury and epithelial reconstitution in the OE. In experimental animal models, toxicants or chemical exposures lead to a rapid degeneration of the normal OE cells, generally sparing some of the basal populations post-injury, as shown. Within days to weeks, stem cells respond to tissue injury to proliferate and produce pools of differentiating precursors, leading to OE reconstitution. As in other self-renewing tissues, stem cells are subject to regulatory mechanisms to maintain epithelial homeostasis. **(B)** OE stem and progenitor cell populations produce the multiple cell lineages in the OE. Several progenitor cell stages are indicated, and are identifiable by expression of specific regulatory factors. Key transcription factors (i.e. Sox2, Ascl1, Neurog1, NeuroD, OAZ), epigenetic modifiers (Bmi1), or growth factor receptors (c-Kit) marking specific cells are indicated. Growth factors and feedback signals, such as ActivinB, BMP4, and GDF11 are not depicted here. Intercellular signaling conveys the status of the OE to basal cells; for instance Notch-Delta signals from the sustentacular cells to the HBCs have been shown to regulate proliferation or dormancy via p63 inactivation.

phenotypes of OE cells and its neurogenic potential. Insights from research with pluripotent stem cells in general, and from cranial sensory placode development in particular, may inform our understanding of adult stem cell biology in the OE.

Olfactory Development and Persistence of Embryonic Features in the Adult OE

While our understanding of the embryonic development of the peripheral olfactory system is incomplete, many details of this complex process have emerged. As with other sensory tissue in the head, one of the earliest events as the three primary germ layers develop is that ectodermal thickenings, or placodes, arise. Cells that comprise these thickenings, such as the otic placodes or the olfactory placodes, begin to express distinct transcription factors, such as Six1 or Eya1.[36] Transcription factors are proteins that orchestrate the expression of target genes, which ultimately result in a given cellular phenotype. Other early placode markers include Pax genes, another key transcription factor family. The olfactory placodes invaginate into pits and, through incompletely understood interactions with underlying mesenchyme and migratory cranial neural crest cells, further inductive events lead to the expression of olfactory-specific developmental programs. It is generally accepted

that the majority of the OE arises from ectodermal placode progenitors, while the underlying lamina propria, including the nonmyelinating Schwann-like cells termed olfactory ensheathing glia, arises largely from neural crest. However, there is some evidence from fate mapping studies that neural crest intermixing with placode may also contribute to a subset of OE cells.[37] Of interest, the gonadotropin releasing hormone (GnRH)-expressing neurons that migrate during development from the olfactory placode region to the hypothalamus arise from neural crest. A developmental failure involving GnRH neurons leads to Kallmann syndrome, or hypogonadotrophic hypogonadism with anosmia, with defects in development of the olfactory bulb and the GnRH cell population.

Many of the inductive or extracellular signals regulating embryonic olfactory neurogenesis have been identified, as well as their downstream effectors. Remarkably, most of these molecular mechanisms remain active in the adult OE, suggesting strongly that these pathways are likely to be clinically relevant (Fig. 2). For instance, the BMP family of growth factors is widely involved in embryonic development, and certain BMP proteins appear to have inhibitory effects on subsets of OE precursors.[38] One of the key transcription factors required for olfactory neurogenesis, Ascl1 (previously known as Mash1), appears to be negatively regulated by BMP4. Ascl1 belongs to the basic helix-loop-helix family of transcription factors and is part of an evolutionarily conserved mechanism regulating neuroectodermal development.[39] Loss of Ascl1 results in severe defects in embryonic development of OSNs and also autonomic neurons.[40] Intercellular signaling, via surface receptors of the Notch family and Notch ligands on neighboring cells, alter the expression of basic helix-loop-helix factors including Ascl and Hes genes to drive differentiation programs, ie, neuronal or non-neuronal fate. Another key feature of early or upstream OE progenitors is expression of Sox2, one of the pluripotency factors identified as necessary for reprogramming adult cells into so-called induced pluripotent stem cells (iPSCs).[41] Evidence suggests that negative feedback signals of the TGFβ superfamily, including ActivinB and GDF11, regulate Sox2 expression, and that accumulation of either Sox2 or Ascl1 in a progenitor cell drives lineage decisions to either sustentacular (glia-like) cells or OSN.[42]

Regulation of Adult Neurogenesis

Using mouse olfactory lesion-regeneration models, the process of adult olfactory neurogenesis has been the subject of considerable study. As stated, many of the molecular mechanisms identified during OE development remain active during adult regeneration. It is well established that during "normal" OSN turnover, it is the globose basal cells that divide to produce new OSNs as needed.[28,31] Even in settings involving widespread loss of OSNs, such as the coordinated retrograde degeneration of the entire OE mature OSN population due to olfactory bulbectomy or nerve section, increased globose basal cell proliferation accounts for the neurogenic response.[18,43,44] As during development, adult globose cells express factors such as Ascl1, other basic-helix-loop-helix proteins, and the surface marker c-Kit.[29,45,46] However, other forms of injury that cause direct epithelial damage that includes a loss of the sustentacular cells situated at the apical layer of the pseudostratified OE, along with OSNs, activate also the horizontal basal cells to proliferate and contribute to reconstitution of the OE.[28,47,48] Interestingly, it is Notch signaling that appears to mediate a feedback cue to the horizontal cells, causing a loss of p63 expression and cell cycle activation.[49] Other regulatory factors identifiable during early embryonic development are active in the adult OE, including the placode markers Six1 and Pax6, as well as the pluripotency factor Sox2, all of which are expressed selectively in the adult basal progenitor and apical glial (sustentacular) layers[34,50,51](Fig. 2). Finally, epigenetic regulatory proteins of the Polycomb group have recently been found to also play a role in adult OE neurogenesis.[34] The Polycomb proteins form complexes that modify chromatin, via methylation or monoubiquitination of specific histone residues, to repress transcriptional programs.[52,53] Polycomb proteins, including EZH2, SUZ12, and BMI1, are key regulators of renewal and differentiation in embryonic stem cells,[54,55] as well as other adult stem cell niches such as the bone marrow and intestinal crypts.[56–58] The expression patterns of these proteins in adult OE, and activity in OE basal cell cultures, is consistent with conserved epigenetic mechanisms regulating OE renewal.[34] In summary, the adult OE is a highly robust neuroproliferative zone, containing both reserve and active populations of stem cells, responsive to feedback cues and multiple regulatory mechanisms to maintain epithelial homeostasis.

Clinical Disorders Causing Anosmia

A range of clinical conditions can contribute to hyposmia or anosmia (Table I). Categories include genetic causes, inflammatory disorders, trauma, or other forms of damage such as post-viral olfactory disorder or presbyosmia.

Genetic disorders

Among the genetic causes of anosmia, Kallmann syndrome, or hypogonadotrophic hypogonadism with anosmia, has been well studied.[59] Several genes have been implicated in causing Kallmann syndrome, including *KAL1*, encoding a cell adhesion protein termed anosmin-1; *FGF8* and *FGFR1,* encoding a fibroblast growth factor and receptor, respectively, that is critical for embryonic neural development; *PROK2*, encoding a prokineticin signaling pathway protein involved in olfactory bulb development; and *CHD7*, a chromodomain protein also known to cause CHARGE syndrome.[60–63] Of interest, CHARGE is also associated with variable sensorineural olfactory loss, likely due to abnormalities in OE basal cell function.[64] Defects due to Kallmann mutations result in failure of proper early olfactory neuron projections from the placode to the olfactory bulb. This impairs

the ability of GnRH-expressing neurons to migrate from the olfactory placode to their destination in hypothalamus, resulting in varying degrees of agenesis of the olfactory bulbs along with hypogonadotrophic hypogonadism. While there is no treatment for the anosmia associated with Kallmann syndrome, early identification is important, since appropriate referral to the endocrinologist can provide hormone replacement therapy.

Ciliopathies are another important category of genetic anosmias. Diseases in which the formation or the function of cilia are impaired have broad clinical manifestations, including renal cysts, hearing and/or vision loss, cognitive deficits, and polydactyly. Olfactory neurons in the OE express OR proteins on their cilia, along with other transduction components, such as olfactory-specific G proteins and ion channels. Therefore, if cilia are absent or malformed, odorant detection cannot occur. For this reason, anosmia is considered a hallmark of cliliopathies.[11,12] Examples of these uncommon disorders include Bardet-Biedel syndrome, Joubert syndrome, and Meckel-Gruber syndrome. Of particular interest, an intranasal viral gene therapy was used to treat a mouse model of a genetic ciliopathy disorder, restoring olfactory neuron cilia morphology as well as olfactory function.[65] Correction of a murine genetic sensorineural anosmia using gene therapy provides evidence that a viral gene therapy approach may be useful for gene delivery to the human OE for certain conditions.

HEAD TRAUMA. Objective smell loss occurs in 15–35% of traumatic brain injury (TBI) subjects.[66] The pathogenesis of head trauma-induced anosmia likely involves several mechanisms. Evidence suggests that blunt trauma causes the brain to move rapidly against the fixed skull base, causing shearing or stretch of the delicate olfactory nerve fibers that project from the nasal cavity through the cribriform plate of the ethmoid bone to connect to the olfactory bulbs of the brain. Furthermore, the trauma can result in bruising or direct injury to the olfactory bulbs, among other intracranial injuries. The end result appears to be a rapid degeneration and death of the primary OSNs, situated in the OE of the nose. Biopsies of human nasal olfactory tissue from post-head trauma anosmia patients often show neurodegenerative changes, strongly supporting the notion that loss of function is related to damage to the OE.[67,68] Despite the ability of basal cells in the OE to produce new neurons, many TBI patients do not regain olfactory function, suggesting that after injury the axons fail to properly reinnervate the olfactory bulbs. Disordered reinnervation has been observed in animal models.[69,70] It is likely that other consequences of trauma such as intracranial scarring, or reactive gliosis, develop and may prevent reinnervation.

POST-VIRAL OLFACTORY DISORDER. Another well described but incompletely understood cause of anosmia or hyposmia is post-viral olfactory disorder (PVOD). It has been estimated that up to 30% of olfactory loss patients may suffer from PVOD.[15] Such patients report an upper respiratory infection or influenza clearly preceding their loss of smell. Despite resolution of nasal congestion and other cold symptoms, anosmia appears to persist. Biopsies of olfactory mucosa from PVOD subjects demonstrate evidence of degenerative changes, consistent with peripheral damage causing loss of function.[15] It is estimated that approximately two-thirds of PVOD subjects experience some improvement over time, but many patients remain anosmic. Although upper respiratory infection is essentially ubiquitous, the reason that some patients develop PVOD is not understood. It is possible that certain genetic factors predispose some individuals to excess OE degeneration, failures in regeneration, or to an inflammatory response that results in excessive OE damage.

SINUSITIS/INFLAMMATION. Decreased olfaction is one of the common complaints associated with active rhinosinusitis. Objective measures report olfactory dysfunction in 30–78% of chronic rhinosinusitis patients, depending upon measurement technique.[71] Indeed, successful treatment of chronic rhinosinusitis can result in objective olfactory improvement.[2,72,73] While obstruction of airflow to the olfactory cleft can cause anosmia, there is compelling evidence that inflammatory cytokines can directly perturb cells within the OE.[74] In mouse models, inflammation can impair OSN function, and prolonged cytokine exposure can cause OSN death.[75] In this model, the typical OE basal cell proliferative response appears abnormally diminished in the presence of ongoing inflammation, but there is recent evidence that steroid treatment to block inflammation also inhibits the proliferation of certain basal cells, and that TNFα receptor 1 may mediate important aspects of basal cell signaling.[76] Thus, both conductive and pleiotropic sensorineural mechanisms can lead to diminished olfaction in rhinosinusitis patients.

PRESBYOSMIA. Several studies have demonstrated that a decline in olfactory function is prevalent among the elderly.[21,77–79] The most recent findings from the U.S. National Health and Nutrition Examination Survey (NHANES), which included measures of olfaction from 1281 participants, identified olfactory dysfunction in 4.2% of subjects age 40–49, 12.7% of subjects age 60–69, and 39.4% of those over 80 years of age.[80] The mechanisms underlying presbyosmia are not fully understood. However, biopsies from olfactory mucosa demonstrate decreased intact neuroepithelium, and increased regions with patches of respiratory epithelium instead of OE.[68] These findings suggest that, in some subjects, there may be cumulative damage leading to neurogenic exhaustion, or a failure of basal stem cells to continue to replace OSNs over time. Olfactory function in the elderly is important for safety, nutritional issues, and quality of life, but anosmia in the elderly has been found, for unclear reasons, to also correlate with increased mortality risk.[22,81]

Treatment strategies, present and future

The treatment of disorders causing olfactory loss remains challenging.[82] In broad terms, goals should include

establishment of a specific diagnosis or cause, if possible; appropriate therapies for any treatable conditions; and proper counseling regarding reasonable expectations and safety issues. The inclusion of objective olfactory measures in rhinology clinical outcomes studies has provided evidence that anosmia or hyposmia due to certain common conditions is often amenable to treatment. For instance, both medical and surgical management of chronic rhinosinusitis can lead to improved olfactory function.[2,73] In appropriate cases in which medical therapy remains ineffective, endoscopic sinus surgery has been shown to improve objective olfactory measures.[3,4]

In cases categorized as sensorineural olfactory losses, such as post-viral olfactory disorder, post-head trauma anosmia or presbyosmia, specific pharmacologic therapies are currently lacking. However, treatment involving intentional repeated exposure to odorants, termed olfactory training therapy, has shown some benefits.[5,83–85] The stimulation of intact OSNs is felt to provide trophic support via activity-dependent mechanisms, and likely also influences synaptic remodeling at the olfactory bulbs.

Ongoing basic research is necessary to identify new treatment strategies for sensorineural anosmias. Many small clinical studies have attempted to test various supplements with little evidence of effectiveness. However, cell culture and animal studies, aimed at understanding the mechanisms involved in damage-induced degeneration and regeneration of the OE by basal stem cells, may provide novel pharmacologic targets. For instance, understanding the signals necessary to activate basal stem cells to proliferate and differentiate may permit the use of agents to promote OE neurogenesis in clinical conditions in which it has malfunctioned. Strategies involving neuroprotective drugs may have a role in preventing excess degeneration in appropriate conditions. Viral gene therapies hold great promise for the treatment of certain disorders, especially genetic diseases involving loss-of-function mutations. Adenoviral based vectors are highly capable of delivering genes to the nasal mucosa, and ease of delivery makes this an attractive strategy. Finally, the translation of cell-based therapies for regenerative medicine has steadily advanced, and has led to clinical trials for the repair of tissues in other organs.[86]

CONCLUSIONS

The peripheral olfactory system is a highly dynamic neuroepithelium lining the olfactory cleft of the nose, from which olfactory neurons project to the brain. Due to their anatomic location exposed to the inspired air, OSNs are vulnerable to damage. The OE appears to retain embryonic-like properties, including populations of neural stem and progenitor cells in the basal layers, providing the tissue an ability to replace OSNs as needed. Nonetheless, a variety of disorders can lead to anosmia, and evidence suggests that OE damage and neurogenic exhaustion may underlie common forms of olfactory loss. Thorough evaluation, including objective olfactory testing, and appropriate diagnosis can direct proper management. Treatment of chronic rhinosinusitis can improve olfactory dysfunction due to obstruction and inflammation, and olfactory training therapy can be of benefit to certain sensorineural hyposmia patients. Ongoing research is necessary to identify new effective treatment options.

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