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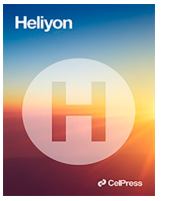

Review article

Olfactory dysfunction and the role of stem cells in the regeneration of olfactory neurons

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ABSTRACT

The prevalence of COVID-19 has drawn increasing attention to olfactory dysfunction among researchers. Olfactory dysfunction manifests in various clinical types, influenced by numerous pathogenic factors. Despite this diversity, the underlying pathogenesis remains largely elusive, contributing to a lack of standardized treatment approaches. However, the potential regeneration of olfactory neurons within the nasal cavity presents a promising avenue for addressing olfactory dysfunction effectively. Our review aims to delve into the current research landscape and treatment modalities concerning olfactory dysfunction, emphasizing etiology, pathogenesis, clinical interventions, and the role of stem cells in regenerating olfactory nerves. Through this comprehensive examination, we aim to provide valuable insights into understanding the onset, progression, and treatment of olfactory dysfunction diseases.

1. Introduction

Olfactory dysfunction stands out as a frequently reported symptom following viral infections, chronic rhinitis, sinusitis, and neurodegenerative diseases. In recent years, the surge in COVID-19 cases has brought heightened attention to this issue among researchers. Despite the generally favorable recovery rates observed in COVID-19 patients, recent investigations indicate that up to 7 % of individuals continue to experience olfactory loss persistently, extending beyond 12 months post-onset of the disease [1]. This protracted olfactory impairment afflicts millions globally, contributing to a substantial decline in the quality of life for those affected. The consequences of olfactory dysfunction are profound, encompassing a significant reduction in appetite, resulting in inadequate and imbalanced food intake, and an overall sense of insecurity among the affected individuals.

Stimulation by various external factors, such as chronic rhinitis, sinusitis, head injury, and neurodegenerative diseases, can cause damage to olfactory neurons. Unfortunately, these damaged olfactory neurons lack the ability to repair themselves, resulting in the manifestation of olfactory dysfunction. Current clinical frontline approaches for treating olfactory dysfunction include drug therapy, surgical intervention, and olfactory training [2–4].

Despite the existing treatment methods, which remain the recommended course of action, researchers are actively investigating

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novel avenues due to the limited effectiveness of available medical options. Recent studies have revealed that basal cells within the olfactory epithelium of the nasal cavity serve as pluripotent stem cells, capable of generating new olfactory sensory neurons [5,6]. Furthermore, various types of stem cells, such as bone marrow mesenchymal stem cells and adipose tissue-derived stem cells, exhibit the potential to regenerate olfactory neurons [7,8]. The induction of olfactory epithelial basal cells to regenerate olfactory neurons represents a promising and innovative strategy for addressing olfactory dysfunction.

Hence, we concentrate on providing a synopsis of the mechanisms underlying olfactory dysfunction and introducing the involvement of stem cells in regenerating olfactory neurons. We begin with an overview of the clinical types, predisposing factors, and pathogenesis of olfactory dysfunction, facilitating a comprehensive understanding of its current status. Following this, we present a summary of prevailing clinical treatments for olfactory dysfunction. Lastly, we underscore the pivotal role and regulatory mechanisms of stem cells in the regeneration of olfactory neurons. This review imparts valuable insights into the onset and progression of olfactory dysfunction diseases, as well as the exploration of future treatment modalities.

2. Generation of olfactory

The olfactory epithelium comprises a pseudostratified columnar epithelial structure primarily consisting of supporting cells (SCs), olfactory sensory neurons (OSNs), and basal cells (BCs) [9,10]. Among these, BCs exhibit stem cell characteristics and are small cells capable of differentiating to replace OSNs or supporting cells lost during normal turnover or injury processes [11]. Based on cell morphology and the expression of specific cell markers, BCs in the olfactory epithelium can be categorized into two distinct cell types: horizontal basal cells (HBCs) and globose basal cells (GBCs) [12]. HBCs reside at the deepest part of the OE basal layer and exhibit a relatively low rate of proliferation without external stimulation. GBCs, situated above the layer of HBCs, represent the primary proliferative population in OE and serve as the main cell population for regenerating OSNs [12–14].

During respiration, olfactory substances in the air interact with olfactory receptors on the outer side of the cell membrane through olfactory sensory neurons. This interaction activates adenylate cyclase in the cell membrane, leading to an increase in cyclic adenosine monophosphate levels, which affects ion channels on the ciliary surface of sensory neurons. Consequently, sensory neurons depolarize, initiate action potentials, and transmit them to the ipsilateral olfactory bulb, ultimately generating olfactory sensation (Fig. 1). OSNs constitute the fundamental units of the olfactory system, and the occurrence of olfactory dysfunction is primarily associated with impairments in the olfactory nervous system, particularly OSNs [15,16].

3. Inducing factors and pathogenesis of olfactory dysfunction

Among patients with olfactory disorders, congenital anosmia has an incidence of approximately 0.01 %. These patients are born without a sense of smell, a condition known as congenital anosmia. In these individuals, the olfactory bulb typically exhibits underdevelopment or regenerative features, often accompanied by a shallow olfactory sulcus [17]. While a small minority of olfactory disorders are congenital, the majority are acquired. Olfactory dysfunction is classified into four main categories based on etiology and anatomical location: sensorineural olfactory dysfunction, conductive olfactory dysfunction, central olfactory dysfunction, and mixed olfactory dysfunction [18]. Sensorineural olfactory dysfunction results from inadequate reception or processing of stimuli by olfactory receptors, OSNs or the central nervous system's olfactory center, often associated with chronic inflammation, diabetes, aging,

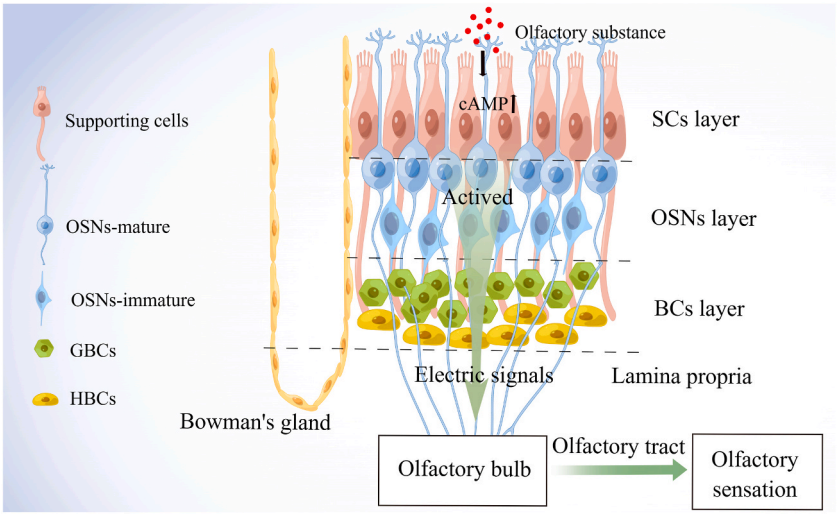

Fig. 1. Pattern diagram of olfactory epithelium in olfactory production. Supporting cells (SCs), olfactory sensory neurons (OSNs), and basal cells (BCs) constitute the olfactory epithelium. The olfactory substances in the air will increase the level of cAMP, depolarization the sensory neurons, and eventually produce the sense of smell.

drug-induced and other factors [19–21].

The most prevalent cause of conductive olfactory dysfunction is obstructive nasal diseases such as chronic sinusitis, nasal polyps, and nasal tumors, which impede odor molecules from reaching or binding to olfactory receptors [22,23]. Central olfactory dysfunction primarily stems from head trauma, neurodegenerative diseases, intracranial tumors, and congenital olfactory abnormalities [24–27]. Additionally, some individuals present with mixed olfactory disorders, exhibiting features of two or more of the aforementioned types. For instance, upper respiratory tract viral infections can precipitate all three types of olfactory dysfunction. The subsequent sections elucidate the primary causes and pathogenesis of olfactory dysfunction.

3.1. Nasal diseases

3.1.1. Chronic sinusitis

Chronic sinusitis, lasting for at least 12 weeks, manifests as inflammation affecting the nasal mucosa and paranasal sinuses. Noteworthy symptoms include nasal congestion, excessive secretion, and a frequently encountered olfactory dysfunction. Even following surgical removal of pathological sinus mucosa in chronic sinusitis cases, persistent and severe olfactory dysfunction is a common outcome [28,29]. The control of inflammation plays a pivotal role in determining the olfactory state of patients with chronic sinusitis. Chronic inflammation disrupts the normal turnover of olfactory sensory neurons, consequently contributing to olfactory dysfunction [30].

Kern et al. conducted a study on olfactory mucosal biopsy in chronic sinusitis patients, revealing that those with decreased olfactory function often exhibit inflammatory infiltration in the olfactory mucosa [31]. Notably, there is a discernible loss of olfactory epithelium with in the inflammatory lesions [32]. Further supporting this, Han et al. demonstrated that olfactory dysfunction in chronic sinusitis (CRS) represents a significant inflammatory olfactory disorder, with inflammation in the cleft palate identified as a recognized cause of olfactory loss in CRSwNP patients [33].

Examining inflammatory damage in a sinusitis model, Egawa et al. compared the extent of damage to the olfactory epithelium and respiratory epithelium. Their findings suggest that olfactory epithelial inflammation stands as another critical pathogenic factor impeding the recovery of olfactory sensitivity [34]. Additionally, research indicates a clear interplay between nasal microbiota imbalance, differential metabolites, and elevated inflammatory mediators in patients with olfactory dysfunction [32].

3.1.2. Allergic rhinitis

Allergic rhinitis is a chronic inflammatory reaction of the nasal mucosa mediated by IgE upon exposure to allergens, involving various immune cells and cytokines. Olfactory dysfunction has emerged as a common clinical symptom of allergic rhinitis [35]. Some studies have indicated that nasal mucosa edema and hypertrophy, along with the obstruction of olfactory molecules reaching the receptors, primarily contribute to the decline in olfaction associated with allergic rhinitis, without significantly affecting the olfactory nerve epithelium [35,36].

Nonetheless, in certain cases, olfactory function remains impaired or incompletely restored even after the removal of obstructive factors. Joel Guss et al. proposed, based on olfactory tests and CT scans, that the olfactory dysfunction in allergic rhinitis may not be linked to nasal mucosa hypertrophy and sinusitis; rather, it may be attributed to the toxic effects of cytokines and inflammatory mediators produced during inflammation on olfactory neurons [37]. Epstein et al. observed in an animal model of allergic rhinitis that prolonged exposure of the nasal mucosa to fungal extracts resulted in significant thinning of the olfactory epithelium and increased density of apoptotic markers within the epithelium, correlating with notable eosinophilic cell infiltration [38]. Cell death, possibly induced by tumor necrosis factor (TNF-α) and interferon-mediated TNF-α, is directly associated with the apoptosis of OSNs [39]. These findings collectively suggest that allergic rhinitis itself can impact olfactory function, with the loss of olfactory function in allergic rhinitis closely tied to the infiltration of inflammatory factors and apoptosis of olfactory epithelial cells.

3.2. Head injury

Injury to any part of the olfactory pathway, from the nasal cavity to the brain, can lead to impairment of the sense of smell. The severity of the head injury, duration of post-traumatic amnesia, type of injury sustained, and age are key factors influencing the presence and extent of olfactory dysfunction [40,41]. Olfactory defects may manifest as conductive or neurosensory, depending on the site of the injury [42]. While conductive defects may be amenable to medication or surgical intervention, sensory deficits often entail limited prospects for recovery. Neurosensory defects resulting from head trauma are notably intricate and typically exhibit poor prognosis for recovery. Currently, a combination of clinical and imaging findings, quantitative assessment, and electrophysiology techniques are employed to ascertain the occurrence of olfactory dysfunction following head trauma. Marin C et al. suggested that the spontaneous recovery and enhancement of olfactory function subsequent to head trauma are associated with heightened subventricular neurogenesis and increased dopaminergic interneurons in the olfactory bulb and glomerulus [40].

3.3. Neurodegenerative diseases

Several studies have reported a correlation between decreased olfactory function and the occurrence of cognitive impairment and related diseases. Olfactory dysfunction can serve as an early marker symptom in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) [43,44]. It has been observed in some studies that patients with AD and PD often exhibit initial pathological changes in the olfactory bulb, characterized by the deposition of AP amyloid protein and tau protein, leading to

olfactory dysfunction [45,46]. The abnormal aggregation of Lewis bodies, arising from the misfolding of alpha-synuclein, along with the deposition of β-amyloid protein and hyperphosphorylation of Tau protein, can contribute to the degeneration and subsequent loss of neurons in critical regions, including the frontal lobe, orbital gyrus, and hippocampus. This process may lead to olfactory dysfunction and cognitive impairment [47]. Besides these pathological processes, abnormalities in the projection pathway of the acetylcholinergic system may also play a significant role in the onset and progression of olfactory and cognitive impairment [48].

3.4. Infection of the upper respiratory tract

The mechanism underlying the loss of olfactory function in patients with COVID-19 in 2019 is highly intricate. SARS-CoV-2 replication in the olfactory neuroepithelium is associated with local inflammation, suggesting that the persistent presence of SARS-CoV-2 and inflammation in the olfactory neuroepithelium may contribute to prolonged or recurrent symptoms of COVID-19, including loss of olfactory function [49]. Besides SARS-CoV-2, influenza virus infection of the upper respiratory tract can also result in loss of olfactory sense, with viruses being detected in the olfactory bulbs and bundles of infected animals. Several studies have demonstrated that influenza virus not only damages the olfactory epithelium but also extends its impact to the olfactory bulb, olfactory tract, and higher olfactory cortex regions via the connection channel between the olfactory epithelium and the central nervous system [50]. In mouse models of virus infection, it has been observed that the damage to the olfactory bulb is more pronounced than that to the olfactory mucosa, indirectly affecting the regeneration of olfactory sensory neurons in the olfactory mucosa and their connection to the olfactory bulb [51].

Furthermore, upon invasion of the olfactory bulb by the influenza virus, alterations in brain cytokines occur, modifying the brain's microenvironment and resulting in olfactory dysfunction [52]. Additionally, infection with Sendai Virus or influenza virus can trigger apoptosis of olfactory sensory neurons while having minimal impact on basal cells, leading to increased apoptosis of olfactory sensory neurons. However, the proliferation of basal cells is insufficient to compensate for the loss of olfactory sensory neurons, resulting in a decrease in the total number of olfactory sensory neurons and subsequent olfactory dysfunction [53]. In summary, this type of olfactory disorder appears to be associated with the infection of the entire olfactory conduction pathway and the survival of olfactory sensory neurons.

3.5. Drug induced olfactory dysfunction

Among the current causes of olfactory dysfunction, drug-induced olfactory dysfunction is often overlooked. Although some drugs have side effects of olfactory dysfunction, there is no clear description in publications. Peter Debbaneh et al.'s survey results showed that from 2011 to 2021, 2450 cases of drugs related to olfactory disorders were reported. Among them, zinc products (370 reports) and fluticasone propionate (214 reports) are most commonly associated with olfactory dysfunction, especially olfactory dysfunction. Antitumor and immunomodulatory drugs account for 21.6 % of olfactory ADR, respectively. In this category, immunoglobulin drugs are most commonly associated with olfactory dysfunction [54]. In addition, the meta-analysis results of corticosteroid treatment for COVID-19 also showed that olfactory dysfunction may be a side effect of this drug treatment method [55,56].

3.6. Other factors

In addition to the more common causes of olfactory disorders mentioned previously, we observe olfactory defects in conditions such as anxiety, depression, schizophrenia, or bipolar disorder [57]. Environmental factors, including air pollutants, may heighten the risk of olfactory dysfunction, potentially attributable to the peripheral inflammatory mechanisms of the olfactory system [58]. Moreover, leprosy (Hansen's disease) correlates with a high incidence rate of olfactory impairment stemming from nasal lesions [59].

4. Clinical treatment of olfactory dysfunction

4.1. Drug treatment

4.1.1. Clinical therapeutic drugs

Glucocorticoids currently represent the most potent anti-inflammatory hormones and demonstrate significant therapeutic efficacy in managing olfactory disorders [60]. A multicenter randomized case-control study conducted by Di Stadio et al. revealed a favorable impact of corticosteroids on long-term olfactory dysfunction in COVID-19 patients [61]. Although animal model studies have demonstrated the beneficial therapeutic effects of steroids in addressing olfactory dysfunction resulting from sinus diseases, the efficacy of steroids in treating post-traumatic olfactory dysfunction in clinical settings remains considerably lower. Optimization of drug duration and dosage is imperative [62,63] L D'Ascanio's clinical trial results showed that the combination of olfactory rehabilitation with oral supplementation of PEA and luteolin is related to the improvement of olfactory function recovery, especially in patients with long-term olfactory dysfunction [64]. Furthermore, careful consideration of potential clinical side effects associated with steroid drugs, such as inflammation, hypertension, and exacerbation of wound infections, is warranted [65,66].

4.1.2. Exploration of therapeutic drug experiments

In addition to the current clinical treatment methods mentioned above, researchers are also continuously conducting experiments to explore new drug treatment methods. Toshiro et al. found that glucocorticoids promote the expression of $Na^{+}K^{+}$-ATPase mRNA in

the olfactory mucosa of rats and facilitate functional recovery after morphological regeneration of the olfactory nerve by regulating ion concentration in the microenvironment of the olfactory mucosa [60]. Lamanthia and colleagues have demonstrated that retinoic acid (RA), a member of the steroid/thyroid signaling molecule superfamily, serves as a significant regulatory factor in morphogenesis, differentiation, and regeneration in mammalian olfactory pathways [67]. However, studies indicate that intranasal corticosteroid treatment for 8 weeks (FP-wk8) can diminish the odor sensitivity of normal mice, suggesting that prolonged intranasal corticosteroid treatment may lead to degeneration of olfactory sensory neurons, thereby affecting treatment efficacy [68].

Growth factors also exert a crucial role in the development of olfactory epithelium and other neural tissues. Research has revealed that fibroblast growth factor 2 stimulates the proliferation of GBCs, transforming growth factor-β2 induces these cells to differentiate into neurons, and platelet-derived growth factors promote the survival of differentiated neurons [69]. Basic fibroblast growth factor (FGF2) fosters the proliferation of GBCs (neuronal precursors in the olfactory epithelium), with endogenous secretion of FGF2 observed in both the olfactory epithelium and lamina propria. These investigations suggest that both the autocrine and paracrine pathways of FGF2 may regulate the development of olfactory nerves [70]. Nerve growth factor has been found to significantly enhance the regeneration of olfactory epithelium in diabetic mice through intranasal instillation by reducing inflammation of diabetes-related cells [71]. VEGF/PDGF combined with growth factor treatment notably increased the number of immature neurons 5 and 7 days after injury, as well as the number of mature olfactory neurons 10 and 14 days after bulbar resection [72]. Although growth factors are mainly utilized in animal models or cell culture experiments for the treatment of olfactory disorders, data regarding their application in clinical treatment is relatively scarce.

Moreover, studies have identified that statins, sodium phenylpropionate, vitamins, ginkgo biloba extract, and the p38-MAPK signal channel inhibitor SB203580 also exhibit certain effects on the treatment of olfactory dysfunction [73–77]. For instance, intraperitoneal injection of statins into mice with anosmia induced by 3-methylindole can effectively repair damaged mouse olfactory mucosa, promote olfactory epithelial proliferation, and facilitate nerve regeneration [73]. Additionally, oral administration of sodium valproate daily to mice with olfactory neuroepithelial degeneration can increase the thickness of olfactory epithelium and the number of OMP positive cells, Ki67 (proliferating cells), and growth-related proteins in mice with olfactory dysfunction, indicating that sodium valproate can promote the regeneration of OSNs [74].

4.2. Surgical treatment

Olfactory dysfunction (OD) constitutes a prominent symptom in CRS, presenting with a prevalence rate ranging from 60 % to 80 % among CRS patients [30]. The impairment of smell can stem from either mechanical obstruction or inflammation of the olfactory epithelium, attributed to conditions such as allergic/non-allergic rhinitis and chronic sinusitis, with or without polyps [78]. Surgical interventions aimed at ameliorating conductive olfactory disorders, such as chronic rhinitis and sinusitis, involve procedures to smoothen the olfactory cleft, facilitating the access of odors to stimulate sensory neurons within the olfactory epithelium [79].

In instances characterized by significant mechanical alterations in nasal airflow and the presence of severe nasal polyps, functional endoscopic sinus surgery demonstrates a capacity to partially alleviate olfactory dysfunction associated with chronic sinusitis. Nonetheless, it is imperative to emphasize the necessity of maximizing the protection of the olfactory mucosa during surgery to mitigate the risk of postoperative adhesion. Additionally, for patients experiencing unilateral hallucinatory qualitative olfactory dysfunction, endoscopic transnasal olfactory epithelial resection emerges as a viable option to alleviate the impairment [80].

The primary challenges confronting surgical interventions for olfactory dysfunction in clinical practice include: 1) Surgical procedures inherently involve a certain degree of trauma, leading to irreversible damage to the olfactory mucosa, with the potential for wound healing complications and re-infection; 2) The postoperative recovery rate of olfactory sensation is suboptimal, accompanied by a notable recurrence rate.

4.3. Olfactory training

Olfactory training, a therapeutic approach, enhances olfactory function by exposing subjects regularly to diverse odors. This method proves beneficial not only in treating patients with olfactory impairment but also in enhancing olfactory capabilities in healthy individuals. The impact of olfactory training on patients with olfactory loss was first reported by Hummel et al. in 2009 [81]. The study involved subjecting patients to twice-daily exposure to four potent odors (phenylethanol: rose, eucalyptol: eucalyptus, citronellal: lemon, and eugenol: eugenol). Olfactory tests, including the phenylethanol threshold, odor recognition test, and odor recognition test, were conducted using “olfactory sticks” before and after the training period. Results indicate that structured, short-term exposure to specific odors can enhance olfactory sensitivity [81].

Furthermore, olfactory training demonstrates efficacy in cases of post-traumatic olfactory loss, showing increased patient test scores (threshold and recognition), intensity ratings, and recognition within functional magnetic resonance imaging scans [82]. Kattar et al. have also highlighted the significant recovery effect of olfactory training on post-viral olfactory dysfunction [83]. The meta-analysis results of the treatment of post viral olfactory dysfunction show that olfactory training is the best recommendation for treating post viral olfactory dysfunction [84], and olfactory training improves olfactory dysfunction caused by COVID-19 [85]. In addition, olfactory training is also a promising way to treat post-traumatic olfactory dysfunction. However, it’s essential to note that research suggests the initial olfactory performance and the underlying causes of olfactory dysfunction are linked to the improvement observed after training [86,87]. Notably, the improvement in olfactory dysfunction following trauma or of idiopathic origin is not substantial. Additionally, challenges such as the prolonged treatment duration, individual variability in effectiveness, and patient compliance pose significant hurdles to treatment efficacy.

4.4. Immunotherapy

Patients with common variant immunodeficiency exhibit an increased susceptibility to olfactory dysfunction compared to their healthy counterparts. Additionally, olfactory dysfunction can be attributed to autoimmune central nervous system inflammation. Immunotherapy serves as a prevalent approach for addressing olfactory dysfunction in immune-related conditions such as allergic rhinitis, chronic rhinitis, sinusitis, and cancer.

In a study conducted by Deniz Tansuker et al., subcutaneous systemic immunotherapy was administered to 12 patients with allergic rhinitis, demonstrating a significant improvement in the olfactory function of these individuals [88]. Further research has indicated that the IL-4/IL-13 receptor antagonist Dupilumab can enhance baseline nasal polyp score (NPS) and nasal congestion (NC), and Lund-Mackay (LMK) and ameliorate olfactory dysfunction scores in patients with chronic rhinosinusitis and nasal polyps who have a history of sinus surgery, as compared to a placebo [79].

Moreover, biological agents targeting different biological markers, such as IL-5, IL-8, and IgE, have exhibited similar effects. Noteworthy examples include mepolizumab, a monoclonal antibody against IL-8, and omalizumab, a monoclonal antibody against IgE [89,90]. Furthermore, immunotherapy-assisted endoscopic sinus surgery has demonstrated efficacy in reducing inflammatory reactions and preventing the recurrence of allergic fungal sinusitis in children [91].

While immunotherapy significantly diminishes the necessity for systemic glucocorticoids and sinus surgery in addressing olfactory dysfunction, its widespread clinical application remains limited. This therapeutic approach primarily targets immune-related diseases associated with olfactory dysfunction, facilitating the recovery of olfactory function by mitigating systemic inflammation. However, the efficacy of immunotherapy in addressing olfactory dysfunction arising from other etiologies appears less pronounced.

5. The role of stem cells in olfactory nerve regeneration

The olfactory mucosa (OM) originates from the olfactory system, serving as a continual source of olfactory nerve sensory cells throughout an organism's adult life. It is regarded as a promising reservoir for cell therapy aimed at repairing olfactory dysfunction [92]. Comprising a diverse array of functional cells, OM primarily includes four types: HBCs, GBCs, mesenchymal stem cells (MSCs), and olfactory ensheathing cells (OECs). Stem cell characteristics are exhibited by the cells within the HBCs and GBCs populations [12]. Moreover, research indicates that both bone marrow mesenchymal stem cells (BMSCs) and adipose-derived stem cells (ADSCs) can expedite the recovery from olfactory dysfunction and play a crucial role in its treatment [93,94].

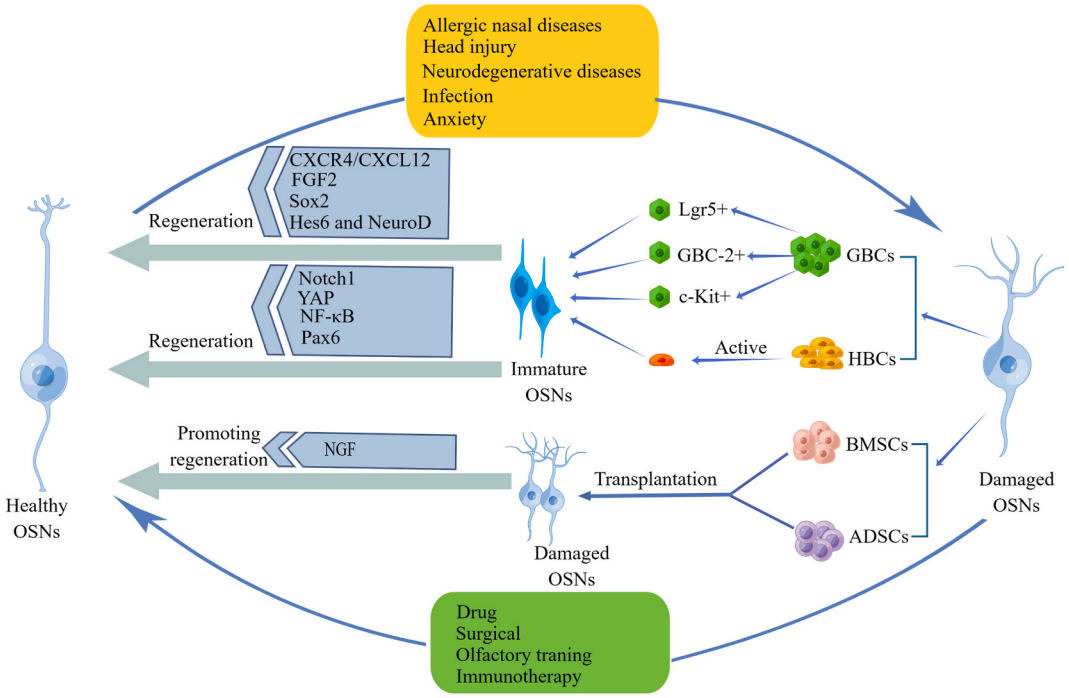

Fig. 2. Repair and regeneration of damaged olfactory neurons. In addition to traditional methods, the potential of stem cells therapy has been discovered. The cells in HBCs and GBCs populations have stem cells characteristics, and BMSCs and ADSCs can accelerate the recovery of olfactory dysfunction. HBCs: horizontal basal cells, GBCs: globose basal cells, BMSCs: Bone Marrow Mesenchymal Stem Cells, ADSCs: adipose derived stem cells.

5.1. GBCs—olfactory epithelial neural stem cells

GBCs constitute a diverse group of cells characterized primarily by the expression of various transcription factors, including Sox2, Pax6, Six1, Ascl1, Neurog1, and NeuroD1 [95–97]. These transcription factors play distinct roles in olfactory development. For instance, Sox2, Pax6, and Six1 predominantly label epithelial cells during the olfactory basal plate/pit stage of embryonic development [95]. In contrast, Ascl1 predominantly marks epithelial cells in the later stages of development [96], and only Six1, Sox2, and Pax6 expressions are discernible in adult epithelial cells [97].

Studies have elucidated the pluripotency of GBCs isolated from the olfactory epithelium. Purified GBCs, isolated using the monoclonal antibody GBC-2 and fluorescence-activated cell sorting, demonstrate the capability to generate GBCs, neurons, supporting cells, and various other non-neuronal cell types upon transplantation [98]. Pulse labeling of GBCs in normal rodent embryonic stem cells, incorporating thymidine analogues, and subsequent "chasing" of markers into their offspring reveal that GBC cell populations act as progenitor cells giving rise to OSNs [99].

Several olfactory bulb-like basal stem cell types expressing markers such as Lgr5, Ascl1, GBC-2, and c-Kit have been identified (Fig. 2). Notably, Lgr5 (+) cells exhibit characteristics similar to circulating stem cells, including Ki67 expression and EdU incorporation. Lgr5 (+) GBCs can regenerate various cell types following normal cell turnover or olfactory lesions [100]. Moreover, the modulation of Wnt signals in the body regulates the function of Lgr5 (+) GBCs, designating them as pluripotent olfactory epithelial progenitor cells [101]. Multicolor fate mapping demonstrates that c-Kit^{+} cells act as transport amplifiers or immediate precursors, contributing to the renewal of olfactory epithelial clones [102]. Comparative analyses of rat olfactory epithelial and respiratory metaplasia regions post-methyl bromide lesions reveal that GBC-2 (+) cells play a pivotal role in regenerating the olfactory nerve epithelium [98]. Collectively, these studies support the contention that GBC subgroups serve as neural stem cells in the olfactory epithelium.

Furthermore, GBCs are subject to regulation by various transcription factors and signaling pathways (Fig. 2). CXCR4/CXCL12 signals emerge as crucial regulators of olfactory neurogenesis, with CXCR4 and its ligand CXCL12 significantly upregulating GBC proliferation during injury-induced regeneration. *In vivo* overexpression of CXCL12 downregulates CXCR4 levels, thereby maintaining GBCs and reducing neuronal differentiation [103]. The transcription factor FGF2 prevents neuronal differentiation and sustains the GBC phenotype [104]. Hes6 and NeuroD, expressed in the olfactory epithelium, vomeronasal organs, and non-sensory plaques, are essential, as their deletion may induce apoptosis in GBCs and OSNs [105]. Under normal or regenerative conditions, over 95 % of Lgr5-EGFP GBCs express Sox2, which plays a regulatory role in the regeneration of GBCs in the olfactory epithelium [5].

5.2. HBCs—olfactory stem cell Repository

The olfactory epithelium (OE) harbors HBCs, functioning as a reservoir of stem cells involved in proliferation and differentiation during OE regeneration. These HBCs represent neural stem cells within the postnatal olfactory epithelium. Research demonstrates that transplanted HBCs derived from tissue can generate diverse OE cell types, including olfactory sensory neurons, supporting cells, and olfactory receptor neurons, and showcasing their pluripotent nature [106]. Notably, HBCs emerge in late development and necessitate activation through substantial epithelial damage to facilitate epithelial reconstruction. For instance, the absence of HBC cilia significantly impedes the regeneration of OSN following lesions [106]. Nevertheless, recent investigations reveal that, even during normal neuronal turnover, HBCs actively generate both neurons and non-neuronal cells throughout adulthood [107]. Following olfactory chemical lesions in elderly mice, HBCs undergo a morphological transition from a flat resting phenotype to a pyramidal proliferative phenotype, indicating that olfactory damage in elderly animals can robustly trigger the activity of dormant HBC stem cells [108]. Additionally, the catabolism of retinoic acid in olfactory sensory neurons enhances the activation of dormant HBC stem cells [109].

The proliferation and activity of HBC neural stem cells are intricately regulated by various transcription factors and signaling pathways (Fig. 2). The transcription factor p63 is crucial for governing the autonomous renewal of olfactory stem cells and has the ability to inhibit HBC differentiation. A decrease in p63 levels prompts the activation of HBCs to an active state in response to OE damage [110]. The downregulation of p63 in lesion-activated HBCs transforms them into pluripotent progenitor cells [111]. These findings suggest that molecular switches dependent on p63 are responsible for activating the reserve stem cell activity of HBCs when required. Notch signaling is essential for maintaining p63 levels, with Notch1 (rather than Notch2) playing a critical role in preserving HBC dormancy after selective neuronal degeneration [112]. OE damage can also lead to the upregulation of proteins (YAP) in HBCs, and activation of YAP proteins through S1P/S1PR2 signals promotes HBC proliferation and OE regeneration after injury. Furthermore, the absence of YAP in HBCs results in impaired OE regeneration and compromised olfactory function recovery post-injury [113]. Acute inflammatory injury in the olfactory epithelium triggers NF-κB-mediated signals, initiating crucial regeneration signals and activating HBC neural stem cells to reconstruct the olfactory epithelium [114].

HBCs in the OE express the epithelial marker keratin 5 (K5) and the stem cell marker Pax6. Notably, specific Pax6 knockout (Pax6-cKO) in HBCs significantly reduces the thickness of OE and the number of regenerated olfactory receptor neurons (ORNs), severely impairing OE regeneration [115]. This emphasizes that the targeted deletion of Pax6 in HBCs significantly hinders the recovery of the olfactory nerve epithelium after injury.

5.3. BMSCs—accelerate olfactory mucosa regeneration

BMSCs possess characteristics of stem cells and progenitor cells, rendering them suitable candidates for cell therapy aimed at restoring olfactory impairment. The unique plasticity of bone marrow-derived cells underscores their potential in this context. In our

study, we transplanted BMSCs into p20 mice, specifically Purkinje cell degeneration (PCD) mutant mice. These mice exhibit a progressive and specific loss of mitral valve cells (MC), a major subgroup of neurons in the olfactory bulb, between p60 and p150 while retaining other major neurons, known as cluster cells [93].

The transplantation of BMSCs influences the recovery of the OE and olfactory function, likely through the regulation of neurotrophic factors, particularly NGF and BDNF (Fig. 2). This modulation suggests novel therapeutic strategies for treating olfactory dysfunction arising from OE degradation. Notably, the research indicates that BMSC transplantation accelerates the regeneration of olfactory mucosa damaged by Triton X-100. In experiments with Sprague-Dawley rats, the olfactory mucosa was irrigated with Triton X-100, and homologous BMSCs were transplanted using phosphate-buffered saline. The results revealed a significantly shortened olfactory recovery time on the BMSCs treatment side, accompanied by increased expression of NGF. The crucial role of NGF in this regeneration process has been documented [7].

Furthermore, co-transplantation of BMSCs and OECs demonstrates notable effects on the recovery of neural function [116]. In a neonatal stroke model of young rats, intranasal BMSC transplantation significantly promotes the recovery of sensorimotor and olfactory functions in neonatal rats [7].

5.4. Adipose derived stem cells—inducing olfactory regeneration

Adipose-derived stem cells possess the capability to secrete various neurotrophic factors crucial for the regeneration of olfactory sensory neurons, including NGF, insulin-like growth factor-1 (IGF-1), interleukin (IL)-15, and brain-derived neurotrophic factor (BDNF) [117,118]· Researchers increasingly favor these cells due to their ease of accessibility and a low incidence rate of donor site complications. Notably, studies demonstrate that ADSCs can induce olfactory regeneration in a mouse model with damaged olfactory epithelium through the secretion of NGF, induced by intraperitoneal injection of methimazole [119].

Furthermore, ADSCs exhibit the capacity to promote the regeneration of olfactory epithelium in mice with unilateral olfactory nerve transection (Fig. 2). In this context, they demonstrate differentiation into olfactory receptor neurons and endothelial cells [94] Transplantation of human adipose tissue-derived stem cells has also been shown to induce olfactory neuroepithelium in a mouse model with permanent olfactory impairment caused by inoculating diclofenac in the dorsal olfactory region [8]. These collective findings underscore the potential of adipose-derived stem cells in inducing olfactory regeneration.

6. Conclusion

The induction of olfactory dysfunction involves a complex array of factors. This article concentrates on elucidating prevalent pathogenic factors and mechanisms associated with olfactory dysfunction, encompassing aging, obstructive nasal diseases, head injuries, neurodegenerative diseases, and upper respiratory tract infections. The aim is to enhance understanding regarding the occurrence and pathogenesis of olfactory dysfunction.

Various methods currently exist for treating olfactory dysfunction. These encompass glucocorticoids and other pharmaceutical treatments, surgical interventions, and emerging therapeutic modalities such as olfactory training and immunotherapy. The latter approaches predominantly find application in treating nasal inflammation. Nevertheless, these clinical treatment options exhibit certain limitations, necessitating continued exploration of novel strategies for olfactory therapy.

Stem cell therapy presents a beacon of hope for patients grappling with diverse diseases, emerging as a promising avenue for treating olfactory dysfunction. However, the intricacies of stem cell biology mandate a comprehensive evaluation of their application in olfactory dysfunction diseases, ensuring a rational and evidence-based therapeutic perspective. Within the olfactory epithelium, GBCs and HBCs are acknowledged as stem cells supporting olfactory nerve regeneration (Fig. 2). GBCs are similar to olfactory progenitor cells, and HBCs serve as a reservoir of stem cells maintaining mitotic inactivity/quiescence in normal olfactory epithelium [12,120]. Studies indicate that injury-induced downregulation of p63 prompts some HBCs to differentiate into GBCs, producing a spectrum of normal epithelial cell types [107]. In addition to olfactory neural stem cells, other stem cell types such as bone marrow mesenchymal stem cells and adipose-derived stem cells have been incorporated into olfactory regeneration research (Fig. 2). As attention to olfactory dysfunction grows, researchers are likely to discover further types of stem cell therapies.

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Consent to participate

It is a review paper. No animals or humans have been involved.

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Pengju Yu: Writing – original draft. **Weiguan Chen:** Writing – original draft. **Ling Jiang:** Software. **Yufeng Jia:** Investigation. **Xiaoyan Xu:** Formal analysis. **Weiye Shen:** Software. **Ni Jin:** Data curation. **Hongjie Du:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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