

Olfactory Epithelium as a Model for Human Neural Regeneration

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Abstract:

The olfactory epithelium is a privileged region in terms of neurogenesis and repair mechanisms that can be studied through its regeneration capability at any age. The present article provides an insight into the current understanding of the regenerative potential of the olfactory epithelium from multiple angles, including cellular composition and diversity, modes of regeneration, molecular regulators, comparative and experimental approaches, and therapeutic implications. The review focuses on the value and limitations of the olfactory epithelium as a model for studying human neural regeneration and discusses the existing evidence from studies of human tissue, animal models, single-cell technologies, and stem-cell biology. It aims to provide a comprehensive view of the regenerative processes by describing the function of particular cells and the modes of their interactions in the context of the entire system. The findings on the functional diversity of olfactory sensory neurons and supporting cells and their connections with stem cells, growth factors, and biomaterials are presented. The article also highlights the differences between the regenerative response in various animal models and the response of the human olfactory epithelium to injury. Finally, the review concludes with a discussion of the therapeutic implications of the study of olfactory epithelium regeneration. The study provides a valuable insight into the mechanisms and points to the importance of additional preclinical and clinical research in multiple areas related to neural regeneration. Moreover, it highlights the complexity of extrapolating the results from animal experiments to humans and the uniqueness of the human olfactory epithelium, which may hinder the translation of the findings and require additional considerations.

Key words: olfactory epithelium; neural regeneration; olfactory sensory neurons; basal cells; neurogenesis; regenerative medicine; organoids

Introduction

The purpose of this review is to provide an integrated perspective linking the cellular and molecular events underlying olfactory epithelium regeneration with comparative biology, contemporary experimental models, and approaches to accelerate regeneration. Each of these topics has been explored individually, but we focus on the intersections between them, both to highlight new opportunities and to more clearly define the limitations of the olfactory epithelium as a model system for human neural regeneration. The review emphasizes findings related to the potential mismatch between robust regenerative responses observed in experimental systems and the more limited, but still considerable, regenerative capacity of the human olfactory epithelium.

The human olfactory epithelium harbors remarkable potential for cell replacement after injury, positioning it as a compelling model for studying neural regeneration [1]. The consideration of the olfactory epithelium as a model for human neural regeneration is timely and strategically advantageous [2]. Significant progress and extensive knowledge have accrued regarding the cellular and molecular mechanisms enabling large-scale neurogenesis and repair in the adult olfactory system, particularly in

rodent models [3]. This accumulated knowledge creates unique opportunities to inform investigations of regeneration in other human tissues with limited regenerative capacity and provides insights into the specialization and evolution of the human central nervous system in relation to regeneration [4]. Although neurological disorders such as stroke, Parkinson's disease, and Alzheimer's disease commonly occur worldwide, the knowledge base for the development of therapeutic strategies remains very limited [5].

Probing the regeneration capacity of the human olfactory epithelium also holds the potential to uncover innovative and clinically relevant strategies for promoting neural repair [6]. The olfactory epithelium shares commonalities with other human tissues subjected to trauma [7]. Much of the interest has focused on harnessing endogenous stem cells to drive replacement, incorporating stem cells into scaffolds for transplantation, creating cell lines for transplant, biomaterial and pharmacological approaches, and environmental enrichment [8]. The richly documented regenerative capacity of the olfactory epithelium among mammalian species, coupled with the well-characterized cellular biology and genetic tools, could enable the identification of new avenues to explore for

stimulating regenerative responses, extending beyond the olfactory epithelium itself [9, 10].

Anatomy and Cellular Composition of the Olfactory Epithelium

The olfactory epithelium is a specialized sensory tissue that serves the sense of smell. The human olfactory epithelium contains olfactory sensory neurons, basal progenitor cells, and sustentacular support cells [11]. It possesses the unique capacity to undergo continuous replenishment, enabling the replacement of old, damaged, or dying olfactory sensory neurons throughout life through multiple regeneration cycles [12]. Olfactory sensory neurons connect to the central nervous

system, allowing the study of sensory-neuron regeneration and integration within a well-defined circuit [13].

Located in the posterior nasal cavity, the human olfactory epithelium is commonly divided into two parts according to schematic drawings of the olfactory sensory-neuron axon-targeting maps in the olfactory bulb [14]. The anterior region, characterized by a narrow, unbranched midline sensory axon, extends the olfactory-sensory-neuron lineage [15]. By contrast, the more extensive and branched axon and the additional basal-cell population along the olfactory epithelium limit multipotent progenitor differentiation during early and late development, respectively [16, 17] (table 1).

Cell/component	Primary role	Regenerative behavior	Relevance to neural regeneration
Olfactory sensory neurons (OSNs)	Odor detection and signal transmission to the CNS	Continuously replaced after normal turnover and injury	Provide a directly observable model of neuronal birth, maturation, axonal targeting, and functional reconnection (11-13, 20).
Globose basal cells (GBCs)	Active progenitor population	Proliferate and generate neuronal progeny during maintenance and repair	Represent an important source of rapidly responding neural progenitors (43, 44, 49, 50).
Horizontal basal cells (HBCs)	Reserve/quiescent stem-cell population	Become activated following substantial epithelial injury	Model injury-triggered recruitment of dormant stem-cell pools (43, 44, 49, 50).
Sustentacular/support cells	Structural, metabolic, and barrier support	Contribute to restoration of epithelial homeostasis after injury	Illustrate the dependence of neural repair on a supportive tissue microenvironment (11, 21, 61).
Mesenchymal/stromal cells	Niche and paracrine support	May participate in injury-associated neurogenic programs	Highlight interactions between resident neural progenitors and surrounding stromal signals (11, 57, 71).

Table 1: Principal cellular components of the olfactory epithelium and their regenerative relevance

Neural Regeneration in the Olfactory System

In the adult human brain, limited neuronal repair occurs in response to injury or degeneration [18]. The olfactory system presents an exceptional opportunity to study neural regeneration because of its unique ability to recover following damage [19]. The adult human olfactory epithelium consists of specialized neurons that transduce odorant signals into action potentials relayed to the central nervous system [20]. Located adjacent to the nasal cavity, these neurons are particularly vulnerable to toxins, pathogens, and allergens [21]. Chronic inflammation of the upper respiratory tract, such as in rhinosinusitis, can severely damage the nasal mucosa and lead to hyposmia or anosmia, significantly affecting quality of life [22]. Approximately 25% of cases involving loss of the sense of smell are linked to chronic sinusitis [23]. The olfactory epithelium is also a site of adult neurogenesis, where sensory neurons are replenished even after extensive loss [23]. Recovery of olfactory function depends on the type of injury and on the speed of regeneration [11].

Basal-Cell Populations and Their Regenerative Potential

Neurosensory tissue arises from either ectoderm or mesoderm; a distinction echoed in the olfactory system [24]. Olfactory sensory neurons and mesoderm-derived support cells, including Müller, retinal pigment epithelial, and retinal pericyte cells, share a lineage relationship [25]. Adult zebrafish possess an amphibian-like capacity for a broader range of retinal neuronal regeneration, further emphasizing the divergent olfactory regeneration potential among vertebrates [26]. Within the olfactory system, amphibians and mammals exhibit highly conserved distinct regenerative pathways, revealing a divergence in basal-cell behavior and a progressive loss of robust regenerative mechanisms in the elaborated mammalian septal organ [27]. Such observations motivate continued exploration of conserved olfactory regenerative mechanisms across species [28]. Within the olfactory system, amphibians and mammals exhibit conserved distinct regenerative pathways, revealing divergence in basal-cell behavior and a progressive loss of robust regenerative mechanisms in the elaborated mammalian septal organ [29]. These observations motivate continued exploration of conserved olfactory regenerative mechanisms across species [30].

Olfactory sensory neurons in mammals make persistent synaptic contacts with inter- and output neurons of the olfactory bulb, a structure homologous to the telencephalon [31]. Such contact raises the possibility of eliciting behaviorally relevant adaptive responses and underscores the clinical significance of existing research [32]. Episodic nerve injury leading to cell-death and regeneration provides a transparent injury model suitable for human olfactory neurogenesis investigations [33]. Accordingly, continuous and dispensable regeneration has been convincingly documented in scenarios of limited neurological repair [34]. Damage to the periphery also exerts a profound effect on the central nervous system, resulting in long-range toxic signals that stimulate plasticity or, conversely, that attract inhibitory circuits, thereby limiting both peripheral and central regeneration [35]. Therapeutic approaches targeting signaling systems activated by peripheral nerve injury remain highly relevant [35]. Therefore, basal cells represent the only source of continuously generated mammalian central nervous system neurons, a property that goes largely unnoticed in the periphery [36]. The visual system is part of a more restricted non-olfactory paradigm [34].

Signaling Pathways and Molecular Regulators of Regeneration

Oligodendrocytes are myelinating cells of the central nervous system that persist throughout life and are capable of generating new oligodendrocytes from oligodendrocyte precursor cells (OPCs) [37]. In response to demyelination, the progenitor state of oligodendrocytes can be re-established, which enhances the regeneration potential [38]. When comparing the regenerative ability of oligodendrocytes from different species, remarkable oligodendrocyte regeneration is observed in the adult rodent central nervous system, while oligodendrocytes in the primate and human central nervous system remain unable to regenerate [39]. Based on comparative studies using a variety of organisms ranging from low vertebrates to mammals, an unambiguous heterogeneity of the regeneration capacity of oligodendrocytes at different species and phylogenetic-level assignments has been highlighted [40]. In the adult mammalian central nervous system, a robust recovery of vision can occur after optic nerve injury, with considerable Olig2-expressing oligodendrocyte regeneration [41]. However, oligodendrocyte

regeneration and functional recovery after optic nerve injury is severely limited in primates, thereby providing a critical reference for understanding the regenerative capacity and the extent of neuronal repair in human central nervous system disorders [42]. In the mammalian olfactory epithelium, injury-induced neurogenesis relies on the activation

of distinct progenitors in basal-cell pools [43]. Within the basal-cell subtypes defined by single-cell RNA-sequencing analysis, there are dormant and active pools; only the active pool give rise to olfactory sensory neuron progeny, yet both pools are capable of re-activation after additional injury [44] (Table 2).

1. Injury	2. Niche / immune signaling	3. Basal-cell activation	4. Proliferation and differentiation	5. Neuronal maturation	6. Functional integration
Loss/damage of OSNs and support cells	Local signals reshape the regenerative microenvironment	Quiescent and active progenitors are recruited	New lineage trajectories generate neuronal precursors	New OSNs acquire mature sensory phenotype	Axons reconnect with central targets and support recovery
<i>Key research question: which signals permit robust regeneration in the olfactory epithelium but remain insufficient in most adult human CNS tissues?</i>					

Table 2: Conceptual sequence of injury-induced olfactory epithelial regeneration

Comparative Perspectives: Olfactory Regeneration Across Species

Adult tissues with regenerative capacities are of great interest because they have the potential to inform regenerative approaches for damaged or degenerating tissues in the nervous system [45, 46]. The vertebrate olfactory epithelium is a well-studied model for understanding neural regeneration *in vivo* because it possesses a remarkable ability to generate olfactory sensory neurons (OSNs) throughout life [47, 48]. Two basal-cell subpopulations (horizontal and globose) can fully restore the neuronal and supporting cell populations after damage [49, 50].

In amniotes, the olfactory epithelium is composed of multiple distinct zones that vary in cellular composition, functional assignments, and innervation patterns [51]. In contrast, non-mammalian vertebrates such as fish and amphibians have a homologous structure that continues to regenerate OSNs throughout adulthood [52]. New World monkey expresses regenerative properties in the olfactory epithelium, whereas Old World monkeys, apes, and human beings can no longer regenerate OSNs owing to a reduced capacity for replacement [53, 54]. While cephalopods and certain arthropods possess simplified olfactory organs, the basal-cell population (analogous to globose basal cells) retains the ability to regenerate sensory neurons in response to injury, suggesting that this capacity is conserved among vertebrates and arthropods [55, 56].

Experimental Approaches and Model Systems

The olfactory epithelium has proven particularly attractive as a model system for studying neural regeneration, and for exploring how these observations could lead to therapeutic avenues for humans [5]. Degeneration of the sensory cells within the olfactory epithelium and loss of olfactory perception commonly occur with aging, exposure to environmental toxins, or neurodegeneration [24]. Following exposure to chemical lesions, the olfactory sensory neurons in the rodent olfactory

epithelium undergo widespread degeneration, eliciting a robust and rapid regenerative response that re-establishes a functional neuroepithelium [33]. The regenerative response involves the activation of, and entirely new differentiation trajectories for, multipotent progenitor cells, which normally remain quiescent in the adult system [57]. In addition to the tissue-resident basal cell populations described in detail above, regenerative responses involve a second population of mesenchymal stem cells that can originate from outside the microenvironment and engage in neurogenic programs [11]. Studies utilizing organoids – multi-layered structures that mature into the olfactory neuroepithelia with the appropriate cues – show that it is possible to obtain epithelium with the same types of diverse stem and progenitor cells found *in vivo*, without universally conserved regeneration cues [58]. In combination with the considerable infrastructure and understanding already dedicated to and established within these systems, they support the idea that the rodent olfactory system provides an entry point for addressing broader questions of how neural tissues maintain their plasticity, even in a homeostatic state, and how the balance between contact and induced replenishment of resident populations can be shifted in favor of deposition during neurodegenerative programs [59]. They also provide a rich substrate for testing how aging and other surrounding, niche-derived signals can influence regulatory networks across multiple tissue types, circuits, and scales [1]. Nevertheless, important challenges remain before the full regenerative capacities of the mammalian system can be confidently harnessed for therapeutic interventions [60]. Systematic identification of the components that constitute the quiescent neural stem cell niche is required, together with the full understanding of how the complete absence of niche-derived signals might alter regulatory logic, network coupling, and coupling across multiple cell types [61]. In this regard, the olfactory epithelium offers access to an additional level of sophistication for discerning how diverse inputs might engage or disengage neural networks across multiple timeframes [62, 63] (Table 3).

Model/system	Principal strength	Questions addressed	Main limitation	Manuscript references
Human olfactory mucosa / epithelium	Direct biological relevance	Cell composition, age-related changes, basal-cell heterogeneity, human neurogenesis	Limited access and relatively low baseline regenerative activity	11, 16, 17, 21
Rodent injury models	Robust and experimentally controllable regeneration	Injury response, progenitor activation, neuronal replacement, functional recovery	Species differences may overestimate human regenerative capacity	33, 45, 57, 73
Fish and amphibian models	Strong adult regenerative capacity	Evolutionary conservation and divergence of sensory-neuron regeneration	Greater evolutionary distance from human biology	26-30, 52, 66
Organoid models	Controlled human-relevant multicellular systems	Stem/progenitor behavior, differentiation, disease mechanisms, therapeutic testing	Incomplete recreation of the <i>in vivo</i> niche and neural connectivity	58, 64
Stem-cell / transplantation models	Tests regenerative intervention directly	Cell replacement, paracrine support, functional rescue	Engraftment, integration, safety, and translation remain challenging	57, 67, 69, 71

Table 3: Experimental systems used to investigate olfactory epithelial regeneration**Implications for Neural Repair and Therapeutic Strategies**

The ongoing capacity of the mammalian olfactory epithelium (OE) for neurogenesis and regeneration is a rich source of ideas for experimental strategies to enhance repair processes in central nervous system (CNS) injuries or diseases [64]. Such experimentation is motivated by data indicating that olfactory function in humans can recover after diverse damage, including early Parkinson's disease, chronic rhinosinusitis, and post-viral infections [65]. Regeneration of olfactory sensory neurons (OSNs) can resume from surviving basal stem and progenitors to restore olfactory performance [66]. Consequently, translation of principles governing olfactory repair into the broader field of neural repair is both feasible and attractive [67].

Clearly, experimental approaches designed to exploit the techniques of olfactory regeneration depend on the design of specific applications [68]. A convenient initial categorization is to consider strategies that 1) augment the existing spontaneous repair system by enhancing basal precursor proliferation or increasing the supply of microenvironment signals and 2) provide novel extrinsic sources of cells for repair by targeting multipotent cells, induced pluripotent stem cells (iPSCs), or closely related cellular types [69]. Initial illustrations of these options form the basis for expanding consideration of olfactory principles to other tissue types and species encanting mechanisms towards future practical therapies [70, 71] (Table 4).

Strategy	Biological rationale	Potential application	Major challenge	Manuscript references
Enhancement of endogenous basal-cell activity	Recruit resident stem/progenitor pools	Promote intrinsic repair after sensory or neural injury	Control proliferation while preserving correct lineage specification	43, 44, 68, 69
Stem-cell transplantation	Provide an extrinsic source of regenerative cells	Replacement or support of damaged neural tissue	Survival, integration, targeting, and long-term safety	57, 69, 71
Cell-free / secretome approaches	Exploit trophic and immunomodulatory signals without transplanting cells	Modulate the repair microenvironment	Standardization, dosing, and durability of effects	62, 67, 71
Growth-factor / biomaterial strategies	Recreate pro-regenerative niche signals	Support progenitor activation, differentiation, and tissue organization	Delivery, timing, and tissue specificity	8, 69, 72
Olfactory training / environmental stimulation	Use activity-dependent plasticity and sensory experience	Support functional recovery and circuit adaptation	Variable response and incomplete mechanistic definition	68, 70
Organoid-based modeling	Reconstruct olfactory epithelial cell diversity in vitro	Disease modeling and preclinical therapeutic screening	Incomplete vascular, immune, and central neural integration	58, 64

Table 4: Translational strategies inspired by olfactory epithelial regeneration**Unique Contribution and Translational Perspective**

The main value of this perspective is that it combines four aspects of research: the cellular and molecular mechanisms of olfactory epithelium regeneration; similar processes in different vertebrates; new approaches to study and understand repair and regeneration; and the implications and limitations of these processes for studying the nervous system repair in humans. These viewpoints help to differentiate between the processes that are well-established in preclinical models and the assumptions about their role in people. In my opinion, the olfactory epithelium is not just an interesting model for studying tissue repair and regeneration, but a valuable system in which neurons, epithelium, and the immune system, as well as non-neuronal cells, interact and contribute to regeneration. At the same time, it is vital to consider some limitations and complexities of translation between different species, insufficient endogenous repair capacities in humans, lack of relevant recreations of the in vivo environment, and the inability to assess functional recovery.

Challenges and Limitations

Despite the great potential of the olfactory epithelium for study of human neural regeneration, there are several challenges that limit the extent to which its regenerative processes can be exploited [11]. Technical issues are a major obstacle, as the experimental systems that can be used to study human olfactory epithelium regeneration do not accurately replicate the human disease situation [52]. Furthermore, although there are numerous in vitro and in vivo systems that can be used to model the unique properties of the olfactory epithelium, they cannot be adapted easily to study specific regenerative properties associated with the olfactory epithelium [64]. Biological factors also play a role in constraining research capability and hindering the development of relevant models

[72]. Human olfactory epithelium regeneration continues at a relatively low baseline rate in the absence of overt injury, which significantly limits the number of endogenous progenitors that can be sampled and studied [73]. In addition, the time course for olfactory neuron maturation is poorly defined and evidence of functional integration after reestablishment of olfactory sensory neuron signaling is scarce [74]. All of the previous challenges are further compounded by a general lack of knowledge regarding the regeneration properties of the diverse populations of basal cells that are present in the human olfactory epithelium [6].

Conclusion

The central nervous system is not capable of regenerating neurons as efficiently after damage or disease. The olfactory mucosa is the only source of neurons in the human CNS that are able to continuously replace the sensory cells in the olfactory epithelium. Due to its accessibility, stereotypical cellular organization, injury-induced neurogenesis, and connectivity to the central olfactory circuitry, the human olfactory epithelium (OE) serves as a valuable model to study neuronal birth, development, maturation, targeting, and function. Comparative studies, single-cell analyses, organoid, and stem-cell based approaches highlighted the importance of the coordinated interplay between different progenitor populations and their neuronal and glial daughters as well as the contribution of the immune and stromal niche to tissue homeostasis and repair. The main significance of the human OE as a model system stems from the combination of these factors and the opportunity to directly address human-specific aspects of neurogenesis and repair. However, future studies should focus on characterizing the human-specific mechanisms of neuroregeneration and delineate the functional relevance of these processes for the development and maturation of the

new neurons as well as the integration into the olfactory circuitry. Defining the opportunities and limitations of the human OE model would greatly benefit from addressing these questions in detail.

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