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Review

Strategies to Develop Regenerative Medicine Approaches for Olfactory Disorders

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Olfactory loss affects more than 12% of the population, with prevalence increasing in aging individuals. Multiple conditions can lead to a loss of smell (hyposmia or anosmia), including post-viral damage from coronavirus disease 2019 (COVID-19) or influenza, head injuries, sinusitis, or neurodegenerative conditions such as Alzheimer or Parkinson disease. Although treatments like surgery, anti-inflammatory medications, or olfactory training can be beneficial in certain cases, there remains an unmet need for effective therapies addressing many common causes of olfactory dysfunction. This is particularly true for cases attributed to damage of olfactory neurons that fail to spontaneously recover. Regenerative medicine approaches, aimed at either stimulating the regrowth of sensory neural structures or replacing them through cell-based therapies, have attracted considerable interest for treating various neurological disorders, including olfactory loss. Here, we summarize the intrinsic regenerative capabilities of the peripheral olfactory system, focusing on current research strategies and the existing barriers that must be overcome for successful translational applications. A major unmet need in this field involves the establishment of reliable and widely accepted culture models for expanding and differentiating olfactory stem or progenitor cells from rodents and humans, both for use *in vitro* assays and as potential material for cell-based therapies.

Keywords. *Smell; Culture; Neurogenesis; Stem Cells; Regenerative Medicine*

INTRODUCTION

Broadly speaking, regenerative medicine approaches may exert therapeutic effects by either delivering signals to endogenous cells in damaged tissues to promote essential processes, such as cell division or differentiation, which have become inhibited or blocked; or delivering exogenous cells capable of engrafting appropriately into damaged tissues, functioning as stem or progenitor cells that can divide and differentiate as needed. In both scenarios, the organ system must be capable of correctly integrating the newly regenerated cells. For example, newly produced olfactory sensory neurons in the olfactory epithelium (OE) of the nose must extend axons through the cribriform plate, enter the central nervous system, and form synapses at appropriate glomeruli in the olfactory bulb of the brain. Because the OE continually generates new olfactory neurons from resident basal stem cells throughout life, evidence suggests that local guidance cues and a permissive microenvironment likely support effective tissue repair [1,2].

The occurrence of adult neurogenesis, whereby olfactory neurons are replaced as needed in the mammalian OE, has been recognized for decades (Fig. 1) [3]. Advances in experimental *in vivo* mouse models have identified two categories of OE basal stem cells and many mechanisms regulating their function. Globose basal cells (GBCs) act as active stem cells; they express the c-KIT receptor along with a cascade of neurogenic basic helix-loop-helix transcription factors and divide as needed to replace neu-

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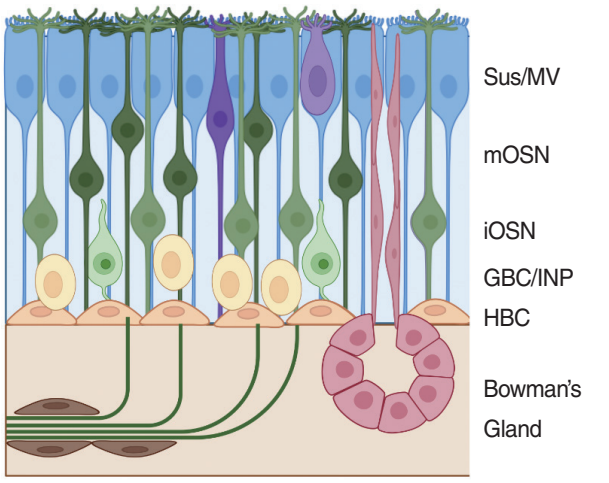

Fig. 1. Schematic representation of the adult olfactory epithelium. The olfactory epithelium lines the superior-most regions of the nasal cavity and consists of sustentacular cells (Sus; blue) at the apical barrier surface, tuft-like and ionocyte-like microvillar cells (MV; purple), mature olfactory sensory neurons (mOSNs; dark green), and more basally positioned immature olfactory sensory neurons (iOSNs; light green). Active stem cells and progenitors, termed globose basal cells and immediate neural precursors (GBCs and INPs; yellow), and reserve stem cells, termed horizontal basal cells (HBCs; orange), are located in the basal layers. The lamina propria underlying the epithelium contains numerous cell types, including immune cells, Bowman's glands, and olfactory ensheathing glia. Olfactory sensory neurons extend dendrites into the nasal airspace, where odor molecules activate specific olfactory receptors on immotile neuronal cilia. Neuronal axons collectively form the fibers of cranial nerve I, projecting to the olfactory bulbs within the brain.

rons through the generation of NEUROD1^{+} immediate neuronal precursors [4-6]. Horizontal basal cells (HBCs), by contrast, remain mitotically quiescent until activated by severe disruptions of the epithelial barrier, thus functioning as reserve stem cells [7-9]. The transcription factor ΔNP63 serves as a master regulator, controlling the quiescence versus activation of HBCs [8,10,11]. Similar to observations in other self-renewing tissues [12,13], the characteristics of OE basal cells appear to differ between steady-state conditions and periods of active tissue repair. Following severe OE injury, evidence indicates the emergence of activated cell states that rapidly re-establish the barrier epithelium and subsequently facilitate ongoing reconstitution of sensory cell populations [14]. Notably, these stem and progenitor populations have also been identified within aging human OE, suggesting that therapeutic approaches aimed at targeting or replacing these cells might be feasible [15].

HIGHLIGHTS

- Decades of research have significantly advanced our understanding of neurogenesis and stem cell capacities within the adult mammalian olfactory epithelium.
- Limited success with olfactory stem cell culture models remains a significant barrier to developing translational therapies for clinical conditions associated with persistent peripheral olfactory system damage.
- Research approaches leveraging recent technological advancements in regenerative medicine are expected to address current challenges, facilitating the development of novel treatments for olfactory disorders.

OLFACTORY CELL CULTURE MODELS

Although *in vivo* rodent experiments have provided detailed insights into olfactory stem cells, widely accepted culture systems remain elusive. Initial olfactory cell culture models were reported several decades ago [16-18]. Early success was achieved using two-dimensional (2D) cultures derived from late embryonic rodent OE explants [16]. This primary culture model reliably produced migratory ASCL1-positive neuroblast cells, a characteristic marker of GBCs, which differentiated for 48 hours before developing into immature neurons. Due to its simplicity and reproducibility, this model yielded numerous insights into GBC regulation. Other studies reported that culturing embryonic tissue in conjunction with olfactory bulb tissues promoted neuronal maturation [18]. However, experiments using dissociated epithelium revealed that cells survived for only a few days, suggesting that specific growth stimuli might be necessary to sustain prolonged cell survival and proliferation. Additional assays characterized the initial effects of signaling molecules such as epidermal growth factor (EGF) and fibroblast growth factor 2 [19,20]. Complete maturation of partially dissociated neonatal rodent epithelium, marked by olfactory marker protein-positive (OMP^{+}) differentiation, was demonstrated using an astrocyte feeder layer, whereas astrocyte-conditioned medium alone was insufficient to achieve full differentiation [21,22]. Subsequent studies utilizing embryonic primary culture models demonstrated that ASCL1-positive GBCs and their immediate neuronal precursor progeny respond to members of the bone morphogenetic protein family. The molecules ActivinβB and growth differentiation factor 11 (GDF11), a ligand within the transforming growth factor-beta (TGF-β) superfamily, were identified as critical negative-feedback signals acting at distinct progenitor cell stages. In the olfactory sensory neuron differentiation pathway, GDF11 feedback limits proliferation of immediate neuronal precursors, whereas ActivinβB inhibits the expansion of earlier-stage GBCs [23].

Another approach involved attempts to generate immortalized cell lines rather than rely exclusively on short-term primary cultures. Although overall success was limited, one spontaneously immortalized rat basal cell-like line was reported [24,25], along with another cell line created through oncogene activation [26]. More recent efforts have focused on purifying rodent olfactory basal cells from dissociated tissue to establish cultures derived from more homogeneous, marker-defined precursor popu-

lations [27,28]. In these studies, GBCs were isolated using distinct cell sorting techniques: one approach employed magnetic-activated cell sorting (MACS) to enrich for adult mouse c-KIT-positive (c-KIT$^+$) cells [2,28], while another utilized fluorescence-activated cell sorting with the monoclonal antibody GBC-2 to selectively isolate GBC populations [27]. Combining purified GBCs with inhibitors of negative-feedback signals allowed the expansion of neurogenic murine basal cells in a 2D culture model across multiple passages [28]. Although this method successfully supported production of olfactory neurons, full differentiation into the OMP-positive state was not reliably achieved. This adherent culture model, along with alternative floating or air-liquid interface methods, permitted at least short-term expansion of neurogenic basal cells, as verified by subsequent *in vivo* engraftment assays [2,29,30].

HBCs, the normally quiescent reserve stem cells, closely resemble keratin-positive (KRT$^+$) and P63-positive (P63$^+$) epithelial stem cells found in other epithelia, such as skin or respiratory epithelium. Using conventional 2D models or air-liquid interface models adapted from established techniques for respiratory epithelial culture, olfactory HBCs from rodent and human biopsy samples have been successfully expanded *in vitro*. Purification or enrichment of HBCs has been achieved based on selective cell adhesion and continued growth under specific culture conditions, or through MACS, which reduces contamination by spindle-like cells [31,32]. Published protocols have employed commercial airway basal media supplemented with suppressor of mothers against decapentaplegic (SMAD) inhibitors, neural supplements, and EGF or TGF-α [31,32]. However, robust differentiation of HBCs into mature olfactory sensory neurons under defined *in vitro* conditions remains unattained. The precise conditions required to activate HBCs and direct them toward a neurogenic differentiation program have yet to be fully elucidated. It is likely that intrinsic (epigenetic) and extrinsic (cell-cell interactions, microenvironmental signals, signaling molecules) cues—both positive and negative—are involved in regulating this process.

ORGANOID MODELS

Across multiple organ systems, a significant advancement in stem cell culture methods has been the development of organoid techniques. Compared to conventional 2D cell cultures, 3D organoid cultures offer a more physiologically relevant microenvironment, better capturing the structural and functional complexity of native tissues. Organoids exhibit enhanced cell-cell and cell-matrix interactions, potentially leading to more accurate cellular differentiation, gene expression patterns, and tissue-specific functionality [33]. Initially developed for cultivating intestinal crypt stem cells within a 3D matrix containing Wnt signaling agonists [34], this approach has since been broadly applied to cultivate stem cells from diverse tissues, including primary tumors and cancer models [35]. A recent report described efforts to cultivate HBCs in a 3D organoid model, which could facilitate advances in manipulating and differentiating this cell population [36]. Other groups have published rodent olfactory culture assays utilizing organoid techniques; however, it remains unclear whether these cultures were initiated from purified basal cells [37-39]. In preliminary studies, we adapted our purified adult mouse c-KIT$^+$ GBC monolayer culture method to a 3D organoid approach (Fig. 2). We found that GBCs purified from chemically lesioned

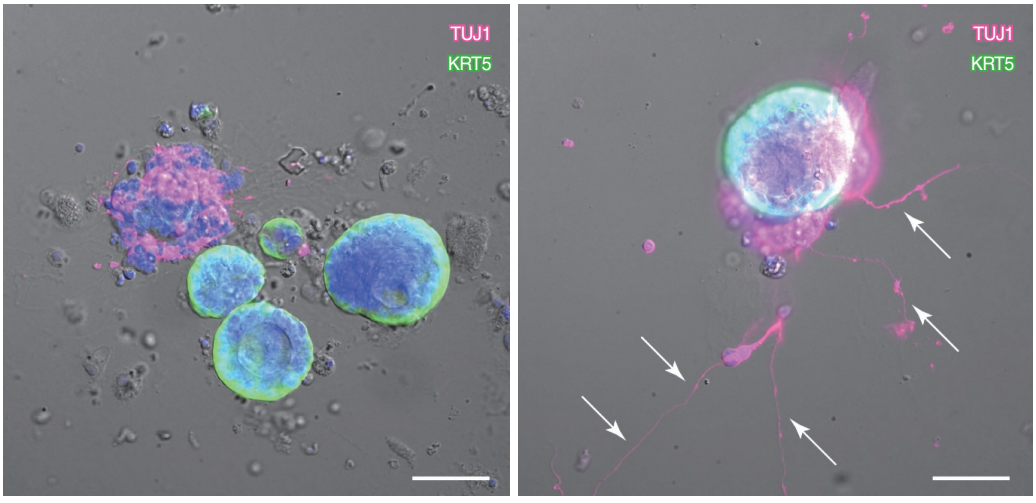

Fig. 2. Purified adult mouse globose basal cell three-dimensional culture model. Adult mouse globose basal cells were purified by immunoselection from dissociated olfactory epithelium using an antibody against c-KIT and subsequently cultured in Matrigel within organoid medium for 1 week. Representative images depict cultures that were fixed and processed for immunofluorescence labeling of neuron-specific class III beta-tubulin (TUJ1; magenta) and keratin 5 (KRT5; green). Under three-dimensional culture conditions, de-differentiated keratin-positive (KRT$^+$) spheres emerged, accompanied by migratory neuron-like cells extending TUJ1-positive (TUJ1$^+$) processes (arrows). Scale bar: 50 μm.

mice following methimazole injection [40] reliably produced spheroids and process-bearing cellular outgrowths. Immunostaining suggests that these GBCs undergo de-differentiation into KRT^+ spheres, with the outgrowth containing neuron-like cells marked by neuron-specific class III beta-tubulin (TUJ1).

OTHER CULTURE MODELS

The term "mesenchymal stem cell (MSC)" refers to a stromal cell population that is readily cultivated from most tissues [41]. Originally described as a bone marrow-derived stromal cell population, MSCs readily adhere to tissue-culture-treated plastic surfaces and rapidly out-proliferate other cell populations in serum-containing media due to their short cell-cycle durations. MSCs lack classic hematopoietic lineage-specific markers and are typically characterized by their capacity to differentiate into cartilage, bone, or fat [42]. Although still debated, evidence suggests that MSC cultures may originate from vascular pericytes [43]. In the olfactory research field, confusion has arisen due to the widespread usage of the term "olfactory stem cell" in reference to MSC-like cultures derived from nasal tissues. Careful characterization has demonstrated that these cultures indeed represent mesenchymal cells rather than genuine olfactory epithelial basal stem cells [44], and they can be derived from non-olfactory regions within the nasal cavity [45]. To date, there is no evidence indicating that nasal MSCs belong to the olfactory epithelial lineage. Although we have attempted to provide a comprehensive overview of olfactory culture models, it is not feasible to include all contributions to this extensive field. We hope this brief review highlights key areas that merit further investigation.

FUTURE RESEARCH DIRECTIONS

Although recent advances have facilitated the establishment of primary olfactory GBC or HBC cultures, their practical utility remains limited by an inability to robustly passage cells or efficiently trigger their differentiation. Additional efforts to characterize and manipulate specific signaling pathways and differentiation factors will be essential to overcome these challenges. Indeed, potential cell-based therapies would require the ability to precisely expand neurocompetent human olfactory progenitor cells, such as GBCs or immediate neuronal precursors. The ability of engraftment-competent GBCs to contribute to functional tissue repair has been demonstrated using a mouse genetic model of inducible hyposmia [2]. This suggests that a similar approach could theoretically be feasible in certain clinical conditions if an analogous cell source were available, such as an autologous reserve cell population capable of expansion in a GBC cell state. In rodents, GBCs exhibit engraftment competence, whereas HBCs demonstrate limited engraftment ability [5]. The transcriptional profile of engraftment-competent cell cultures has previously been assessed [2].

An alternative approach to generate human GBCs *in vitro* could involve the use of pluripotent stem cells, such as embryonic stem cells or induced pluripotent stem cells derived from the reprogramming of somatic cells [46]. Given their broader differentiation potential compared to adult tissue-specific stem cells or MSCs, and the capability to direct pluripotent stem cells toward specific germ-layer fates, embryonic stem cells or induced pluripotent stem cells could theoretically produce cells of the olfactory neuronal lineage. Indeed, significant advancements have been achieved in directing pluripotent stem cells to differentiate into inner ear, retinal, and peripheral sensory structures [47-50]. However, efficient culture conditions for guiding pluripotent stem cell differentiation specifically toward an olfactory epithelial lineage have yet to be established. Nevertheless, the potential capability to generate olfactory cells autologously—similar to reported advancements with other cranial sensory placode-derived lineages—is an appealing aspect of cellular reprogramming for developing cell-based therapies.

In summary, decades of research have yielded remarkable insights into the regenerative capacities of adult OE. Advances in 3D cell culture techniques and cellular reprogramming for controlling cell states and manipulating differentiation have proven beneficial in numerous fields. Given the significant unmet clinical need for effective olfactory disorder treatments, continued efforts to apply regenerative medicine research advancements remain a high priority.

CONFLICT OF INTEREST

Do Hyun Kim is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported. BJG is co-founder of Rhino Therapeutics. No other potential conflicts of interest relevant to this article were reported.

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Conceptualization: BJG, DHK, DWJ. Methodology: DHK, MW, TK. Data curation: DHK, SK. Project administration: BJG, DWJ. Visualization: DHK. Writing–original draft: DHK. Writing–review & editing: DHK, BJG, TK, MW, SK. All authors read and agreed to the published version of the manuscript.

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