



REVIEW

Research on the Construction and Application of Organoid-Based Bionic Nasal Mucosa

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ABSTRACT: The nasal mucosa, serving as the primary interface of the respiratory tract, performs essential functions including air conditioning, immune defense, and olfaction. However, traditional *in vitro* and animal models fail to fully recapitulate its complex cellular composition and physiological microenvironment. The emergence of organoid technology offers a revolutionary approach to construct high-fidelity bionic nasal mucosa models. This article reviews recent progress in the establishment of nasal mucosa organoids established from adult stem cells and pluripotent stem cells, outlining key culture conditions including extracellular matrix and specific growth factors. We further discuss emerging bioengineering approaches for improving organoid sophistication, including multicellular co-culture systems, microfluidic platforms, and organ-on-chip models, which facilitate the simulation of dynamic biological and biomechanical conditions. The applications of these models in fundamental biological research, disease modeling, including genetic airway diseases, viral and bacterial infections, and drug screening are comprehensively reviewed. Finally, we address current challenges such as vascularization and immune cell integration, and propose future directions for multidisciplinary convergence to advance nasal mucosa research from basic science to clinical translation.

KEYWORDS: Nasal mucosa organoid; microfluidics; organ-on-a-chip; bionic; disease modeling

1 Introduction

The nasal mucosa is a specialized tissue comprehensively covering the surface of the nasal cavity and extending into adjacent areas such as the paranasal sinuses and nasopharynx [1]. As the primary gateway of the respiratory system, it performs critical physiological functions, including regulating the temperature and humidity of inhaled air, forming a robust physical immune barrier, and facilitating delicate olfactory perception [2]. Based on histological characteristics, this tissue can be divided into two major functional regions. The olfactory mucosa, located in the middle portion, accomplishes the identification, conversion, and neural transmission of odor signals through its pseudostratified columnar epithelial structure and specialized cell populations, such as supporting cells and olfactory sensory neurons. Meanwhile, the respiratory mucosa establishes an efficient mucociliary clearance mechanism through the coordinated action of mucus secretion by goblet cells and ciliary beating by ciliated cells, continuously defending against the invasion of external pathogens [3]. However, traditional research models exhibit significant limitations when simulating these complex physiological and pathological processes. Although immortalized cell

lines are convenient, they tend to lose cellular heterogeneity after prolonged passage [4]. Primary cells face challenges like limited sources and dedifferentiation, while animal models struggle to accurately reflect human-specific immune responses due to inherent species differences [5]. Therefore, these specific requirements for modeling pseudostratified architecture, multicellular coordination, and barrier integrity drive the demand for enhanced model capabilities and more advanced *in vitro* biomimetic platforms.

The emergence of organoid technology has revolutionized fundamental research and translational applications concerning the human nasal mucosa. Nasal mucosa organoids are essentially sophisticated three-dimensional self-organizing cultures established using different stem cell populations, such as pluripotent and adult stem cells, which reconstruct miniature tissues *in vitro*. These highly structured organoids fundamentally possess the key distinct cell types, complex spatial architecture, and essential physiological functions of the original organ [6]. In this context, the innovative concept of “bionic nasal mucosa” proposed in this paper emphasizes not only the precise simulation of the physical and morphological structure of the nasal cavity but also focuses intensely on reproducing its dynamic physiological functions, cellular heterogeneity, and complex tissue microenvironments involving epithelial-mesenchymal interactions. The ultimate goal is to establish a long-term *in vitro* mucosal model system that more closely resembles human functions [7]. General traditional two-dimensional cell cultures or simple transwell systems only serve as temporary or overly simplified substitutes, which lack multicellular coordination and are less involved in replicating the authentic host-pathogen interactions [8]. In comparison, such multifunctional bionic organoid models can help to mimic the various pathological states of nasal diseases and accurately regulate the physiological process of mucosal homeostasis, ultimately providing superior biomimetic performance compared with conventional platforms. Hence, highly biomimetic nasal mucosa organoids serve as powerful platforms for respiratory research and related drug development.

In this review, we summarize the advantages of organoid engineering and biofabrication technologies in promoting human nasal mucosa research (Fig. 1). First, we introduce several fundamental concepts to facilitate understanding of the principles of organoid construction using different seed cell sources, followed by major factors affecting the reproduction of mucosal functions. Various preparation approaches and typical bioengineering strategies for constructing bionic nasal mucosa organoids are then systematically introduced. These advanced strategies encompass the integration of complex cellular compositions, the incorporation of microfluidic technology, the development of sophisticated organ-on-a-chip platforms, and the synergistic application of advanced biomaterials. Next, we highlight the remarkable application progress of these functional models in fundamental biomedical research, emphasizing disease modeling for conditions such as allergic rhinitis and viral infections, as well as high-throughput drug screening and regenerative medicine. Finally, the possible developmental direction and current technical bottlenecks, such as the distinct lack of vascularization networks and the insufficient functional integration of immune cells, are also comprehensively analyzed. By envisioning future directions through multidisciplinary convergence and biomaterial innovation, we aim to provide a robust theoretical framework and technical pathway. We anticipate this review will provide readers with deeper insights into bionic nasal mucosa organoids while facilitating future clinical applications for a wide range of nasal disorders.

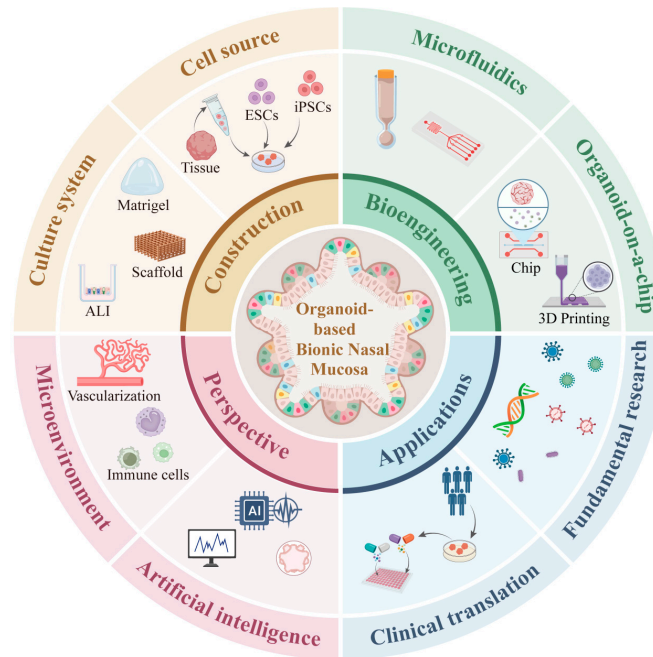


Figure 1: Overview of the construction and applications of organoid-based bionic nasal mucosa.

2 Cultivation and Expansion of Nasal Mucosa Organoids

The successful construction of nasal mucosal organoids hinges on simulating and reconstructing the ecological niche of nasal mucosal stem cells *in vivo* within an *in vitro* environment [9,10]. This niche is jointly defined by specific cell sources, extracellular matrix, growth factors, and signaling pathways, guiding cells to self-organize into miniature organs that possess the key structural and functional characteristics of their *in vivo* counterparts [11]. This section will systematically elaborate on the seed cell sources and critical culture conditions for nasal mucosal organoids.

2.1 Sources of Nasal Mucosa Stem Cells

The cellular composition of the airway epithelium, including basal epithelial cells, secretory epithelial cells, club cells, and tuft cells, provides the structural basis for selecting appropriate seed cells for nasal mucosa organoid construction (Fig. 2a) [12].

2.1.1 Adult Stem Cells

The construction of nasal mucosal organoids begins with seed cells possessing self-renewal capacity and multipotent differentiation potential. Based on their developmental stage and origin, these cells can be generally divided into adult stem cells (ASCs) and pluripotent stem cells (PSCs) [13]. ASCs derived from nasal tissue represent the most direct cell source for the generation of nasal mucosal organoids. Basal cells expressing canonical markers such as p63 and KRT5, which can be isolated from nasal brushings or surgical specimens, constitute the principal stem cell population [14–16]. Consistently, Chiu et al. established expandable nasal organoids from nasal swab-derived epithelial cells and further induced them into three-dimensional differentiated organoids or differentiated nasal organoid monolayers, demonstrating a practical strategy for adult stem cell-derived nasal mucosa organoid generation (Fig. 2d) [17]. Under appropriate three-dimensional (3D) culture conditions, these cells are capable of sustained proliferation and, upon

exposure to specific differentiation media, can differentiate into all major respiratory epithelial lineages, including ciliated cells, goblet cells, and basal cells [18].

Additionally, the olfactory mucosa contains two major basal cell subtypes, one being globose basal cells (GBCs) and the other horizontal basal cells (HBCs) [19]. GBCs are the primary, actively proliferating progenitors capable of generating olfactory sensory neurons and supporting cells, while HBCs function as quiescent stem cells activated upon severe injury [20]. Although olfactory organoid development has lagged due to the difficulty of precise tissue acquisition from the olfactory cleft, successful cultures of organoids containing immature neurons from mouse and human samples hold great promise for modeling neurodegenerative diseases and olfactory disorders. Meanwhile, Lin et al. established surface airway epithelial and submucosal gland organoids from human bronchus tissue, showing that distinct airway epithelial compartments can be separately isolated and expanded while retaining region-specific cellular characteristics (Fig. 2c) [21].

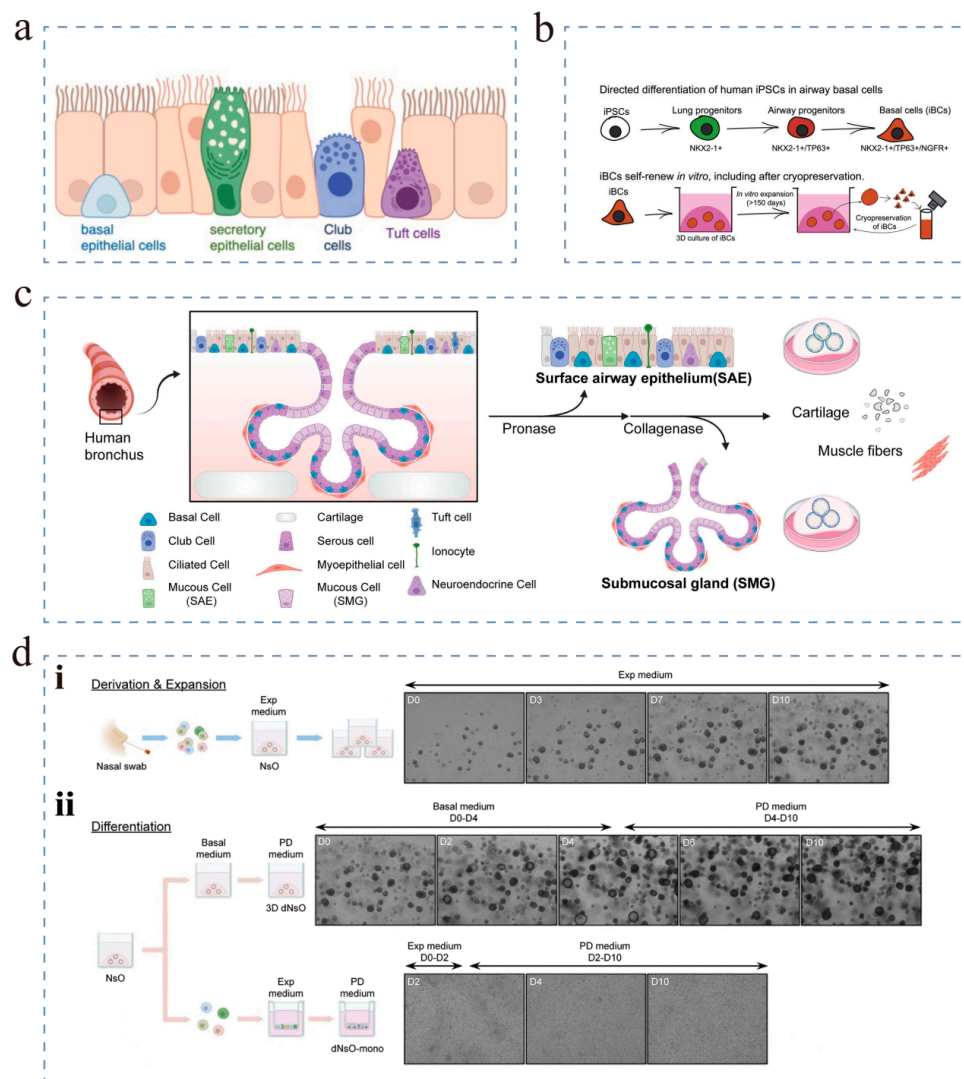


Figure 2: Cellular sources and culture routes for nasal mucosa organoids. **(a)** Major epithelial cell types in the airway epithelium [12]. Copyright 2022, the authors. **(b)** Directed differentiation of human iPSCs into airway basal cells, which possess self-renewal capacity and multilineage differentiation potential [22]. Copyright 2020, Elsevier Inc.

(c) Schematic illustration of the isolation of surface airway epithelium and submucosal glands from human bronchial tissue for organoid culture [21]. Copyright 2025, the authors. (d) Establishment of nasal mucosa organoids from nasal swab-derived epithelial cells, followed by (i) expansion ($\times 40$) and (ii) differentiation ($\times 40$ for 3D organoids and $\times 100$ for organoid monolayers) [17]. Copyright, 2022 Chiu et al.

2.1.2 Pluripotent Stem Cells

PSCs encompass two major categories, one being embryonic stem cells (ESCs) and the other induced pluripotent stem cells (iPSCs), which represent a promising alternative cell source for nasal mucosa research [23]. The emergence of iPSC technology constitutes a breakthrough in the field. Hawkins et al. demonstrated that human iPSCs can be directed stepwise into lung progenitors, airway progenitors, and induced basal cells with self-renewal capacity, supporting PSC-based generation of airway epithelial stem cells (Fig. 2b) [22]. Derived from somatic cell reprogramming, iPSCs address the ethical controversies associated with human ESCs and the limitations of invasiveness and finite supply inherent in adult stem cell sourcing [24,25]. iPSCs offer a virtually unlimited cell source while retaining the donor's genetic background, enabling the establishment of large-scale disease biobanks and facilitating personalized disease modeling and drug screening [26,27].

The directed differentiation of PSCs toward nasal epithelial lineages follows developmental principles associated with surface ectoderm specification. In contrast to endoderm-derived airway systems, this process is thought to involve sequential transitions through non-neural ectoderm and pre-placodal ectoderm (PPE), ultimately giving rise to olfactory or nasal placode progenitors [28]. This differentiation trajectory is regulated by the coordinated modulation of key signaling pathways, including BMP, WNT, and FGF, with precise temporal control of BMP activity being particularly critical for placodal specification [29,30]. Although current PSC-derived nasal organoid models do not fully recapitulate the complete developmental hierarchy observed *in vivo*, these approaches provide a conceptual framework for reconstructing nasal epithelial lineages. As such, PSC-based systems offer significant potential for investigating early lineage specification, modeling congenital nasal disorders, and enabling scalable, patient-specific applications. Therefore, while ASC-derived organoids more directly model adult tissue homeostasis, PSC-derived models provide complementary advantages in developmental studies and genetic disease modeling.

2.2 Key Cultivation Conditions

The successful cultivation and long-term expansion of nasal mucosa organoids critically depend on a culture system that accurately recapitulates the *in vivo* stem cell niche. This system primarily consists of an extracellular matrix (ECM) that provides physical support and biochemical cues, together with a highly specialized culture medium (Fig. 3).

2.2.1 Extracellular Matrix

The ECM serves as a critical physical foundation for the three-dimensional growth of organoids. Beyond providing a structural scaffold for cell aggregation, the ECM delivers complex biochemical signals through integrin receptors, which are essential for regulating cell survival, proliferation, and the establishment of apicobasal polarity. Currently, Matrigel remains the most commonly used ECM and is obtained from the Engelbreth-Holm-Swarm (EHS) mouse sarcoma as a basement membrane extract [31,32]. This complex mixture is highly enriched with laminin, collagen IV, and entactin, alongside various endogenous growth factors, allowing it to closely mimic the physical and biochemical properties of the native sub-epithelial basement membrane. Such an environment effectively promotes the self-organization and 3D structural

assembly of nasal epithelial cells [33,34]. The standard initiation step involves embedding isolated nasal mucosal stem cells or lineage-committed progenitor cells within a Matrigel droplet, which is then thermally solidified to initiate organoid formation [35]. This Matrigel-embedding strategy is consistent with the workflow summarized by Ekanger et al., who compared Matrigel-based airway organoid culture with ALI Transwell culture and highlighted their differences in cell source, culture configuration, differentiation time, and maintenance requirements (Fig. 4b) [36].

Despite its effectiveness, Matrigel exhibits significant limitations including batch-to-batch variability, animal-derived origins, and an undefined molecular composition, all of which hinder experimental reproducibility and complicate clinical translation in regenerative medicine [37]. Decellularized nasal mucosa-derived extracellular matrix may provide an alternative scaffold for nasal mucosa organoid culture by preserving tissue-specific ECM components and biochemical cues of the native mucosal microenvironment. Such matrices may therefore offer a more physiologically relevant niche to support organoid growth and differentiation, although further optimization and standardization are required for their application. Consequently, the development of defined and tunable synthetic hydrogels has become a primary focus in the field. These advanced biomaterials, such as recombinant protein scaffolds or polyethylene glycol-based matrices, enable fine regulation over mechanical stiffness and degradation rates [38]. Furthermore, they can be functionalized with specific bioactive motifs, including RGD peptides and laminin-derived sequences, to provide superior guidance for the functional maturation of nasal mucosa organoids [39,40].

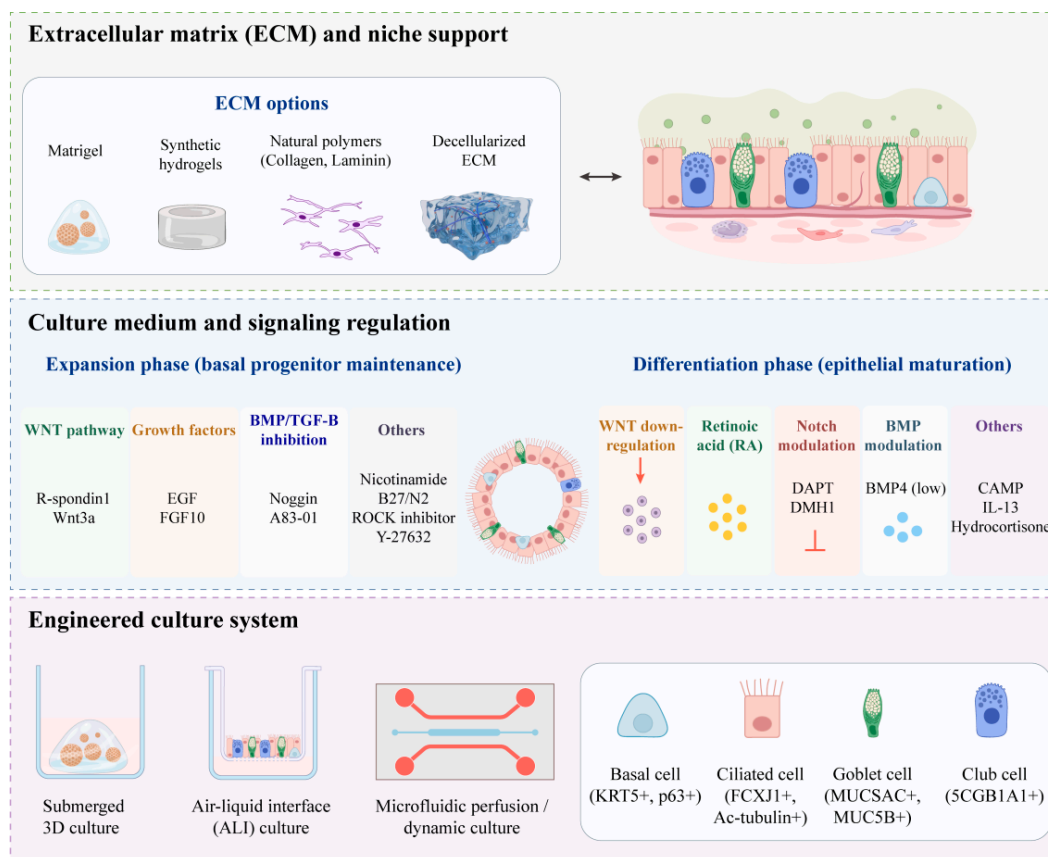


Figure 3: Schematic overview of extracellular matrix support, culture medium regulation, and engineered systems in nasal mucosa organoid cultivation.

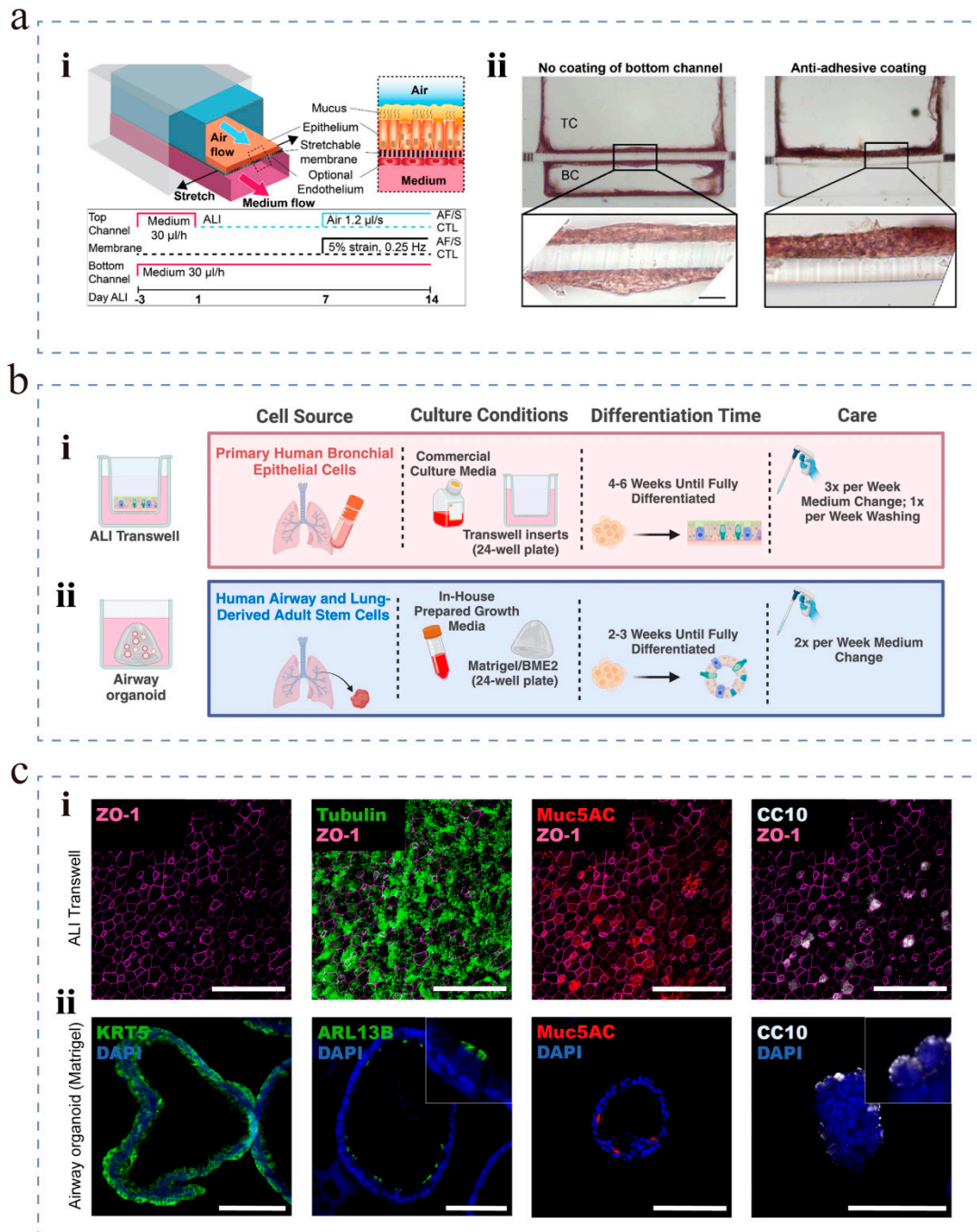


Figure 4: Culturing and characterization of human airway and nasal organoids. **(a)** Airway-on-chip culture system. **(i)** Schematic of the airway-on-chip culture system and **(ii)** histological validation of bottom-channel anti-adhesive coating. (scale bar, 50 µm) [41]. Copyright 2023, the authors. **(b)** Comparison of ALI Transwell and Matrigel airway organoid culture workflows. **(i)** ALI Transwell culture workflow. **(ii)** Matrigel culture workflow [36]. Copyright 2025, the authors. **(c)** Characterization of airway epithelial architecture and cell-type composition. **(i)** Immunofluorescence images of ALI Transwell cultures showing ZO-1, tubulin, Muc5AC, and CC10. (scale bars, 50 µm) **(ii)** Immunofluorescence images of Matrigel cultures showing KRT5, ARL13B, Muc5AC, and CC10. (scale bars, 100 µm) [36]. Copyright 2025, the authors.

2.2.2 Specialized Culture Medium

The biochemical composition of the culture medium is the decisive factor in determining organoid cell fate, necessitating a precise balance between stemness maintenance and directed differentiation [42]. Optimized media for nasal mucosa organoids generally utilize a nutrient-rich basal formulation, such as DMEM/F12, supplemented with a specific combination of growth factors and signaling modulators. The maintenance of the basal progenitor pool relies heavily on WNT pathway activation together with the simultaneous suppression of pro-differentiation signals [43]. R-spondin 1 acts as a potent WNT enhancer by stabilizing β -catenin, which is essential for long-term expansion, while Noggin serves as a BMP signaling antagonist to prevent premature differentiation [44]. Crucially, the inclusion of TGF- β inhibitors is often required to sustain the proliferative capacity of p63-positive basal cells and prevent squamous metaplasia. Furthermore, Epidermal Growth Factor (EGF) and Fibroblast Growth Factor-10 (FGF-10) are integrated to stimulate epithelial cell survival and homeostatic growth [45]. To further support metabolic requirements, the medium is enriched with N2 and B27 supplements, providing essential lipids, hormones, and trace elements, alongside Nicotinamide to enhance cellular longevity [46]. During the vulnerable stages of passaging or single-cell seeding, a ROCK inhibitor is routinely added to the medium to suppress the Rho-associated coiled-coil kinase pathway, thereby preventing anoikis and significantly improving clonal formation efficiency [47].

The standard cultivation protocol involves suspending cells in liquid Matrigel for plating, followed by thermal polymerization at 37°C and the addition of the complete expansion medium [48]. Once the organoids reach their optimal size, they are dissociated via mechanical or enzymatic methods for re-embedding and passage. Functional maturation is subsequently achieved through a dedicated differentiation phase. By withdrawing stemness-maintaining factors like Noggin and R-spondin 1, and introducing maturation-promoting agents such as all-trans Retinoic Acid, the organoids are directed to develop specialized structures, including motile cilia and secretory cells [49]. Ekanger et al. verified the expression of ZO-1, tubulin, ARL13B, MUC5AC, and CC10 in ALI- and Matrigel-cultured organoids by immunofluorescence staining, confirming the formation of epithelial barrier structures, ciliated cells, goblet cells, and club cells (Fig. 4c) [36]. In addition, to better mimic the *in vivo* airway microenvironment, Nawroth et al. established a microfluidic airway-on-chip system that integrates airflow, medium perfusion, and cyclic mechanical stretching into *in vitro* culture (Fig. 4a) [41]. This system introduces biomechanical cues and enables a more physiologically relevant airway epithelial model. This modular culture strategy can also be used to model specific physiological or pathological conditions. For example, the addition of interleukin-13 an inflammatory inducer, can promote goblet cell hyperplasia [50]. Alternatively, exposure to allergens such as house dust mites on the apical surface can be applied to establish *in vitro* organoid models of airway inflammation [51,52].

2.3 Characteristic Identification of Nasal Mucosa Organoids

To ensure that nasal mucosa organoids constructed *in vitro* can accurately mimic key features of the native tissue, they need to be characterized from multiple aspects. This typically includes the evaluation of their morphological structure, cellular composition, specific markers, and physiological functions [53,54].

2.3.1 Morphological and Ultrastructural Analysis

Morphological characterization is the basis for validating organoids. Light microscopy can be used to dynamically observe overall structural features, including size and cystic or solid density, providing a direct assessment of growth status [55]. For example, bright-field imaging can monitor the gradual growth and expansion of nasal mucosa organoids at different culture stages. At the same time, differentiation

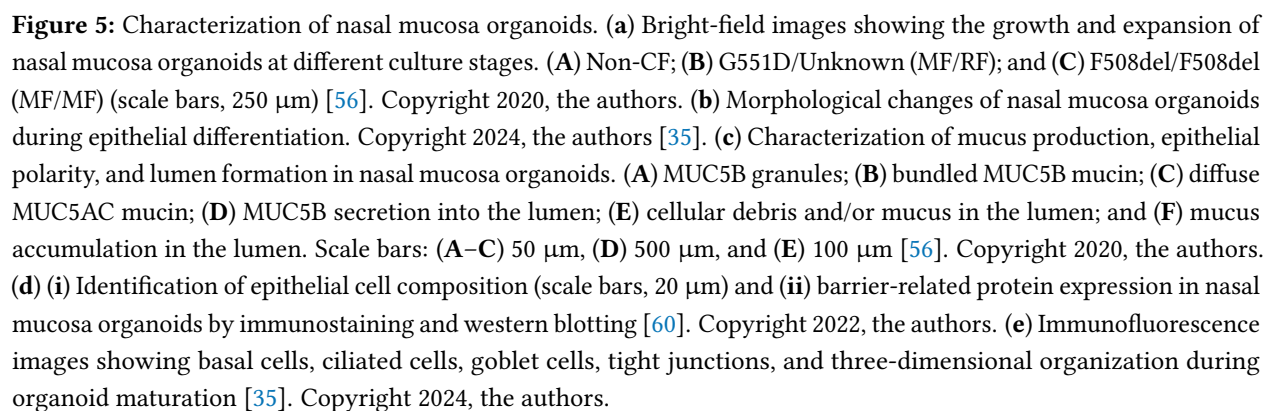
is accompanied by clear morphological changes, such as increased organoid size, lumen formation, and gradual structural maturation (Fig. 5a,b) [35,56]. To examine more detailed internal structures, histological methods such as hematoxylin and eosin staining are commonly used to evaluate nuclear–cytoplasmic distribution and tissue organization [57]. Immunofluorescence staining allows high-resolution localization of cell-specific proteins [58]. In differentiated nasal mucosa organoids, commonly used markers include acetylated α -tubulin for identifying mature ciliated cells, MUC5AC for secretory goblet cells, and ZO-1 or E-cadherin for visualizing intercellular junctions (Fig. 5c–e) [22,35,56,59,60]. Together, these markers confirm the reconstruction of the pseudostratified epithelial structure and its barrier function. In addition, scanning electron microscopy can be used to observe the density and distribution of cilia on the luminal surface (or the outer surface in apical-out configurations) (Fig. 6a) [61]. Transmission electron microscopy further reveals ultrastructural features, such as the typical “9 + 2” microtubule arrangement within cilia, providing structural evidence for the functional maturity of nasal mucosa organoids (Fig. 6b) [62].

2.3.2 Analysis of Molecular Marker Expression

Molecular profiling is central to confirming cellular heterogeneity and differentiation states [63]. Common techniques include quantitative real-time PCR (qRT-PCR), western blotting, and bulk RNA sequencing, which are used to batch-detect the expression of specific markers (Fig. 5d(ii)) [60]. Markers for nasal mucosa organoids include p63 and KRT5 for basal progenitor cells, FOXJ1 and DNAH5 for ciliated cells, and MUC5B or SPDEF for goblet cells [22,59]. Beyond bulk analysis, the application of single-cell RNA sequencing enables precise dissection of transcriptomic features and the ratios of subpopulations within the organoid at single-cell resolution [64]. Comparing these high-dimensional data with transcriptomic profiles of native nasal mucosa tissue provides a comprehensive assessment of the model’s biomimetic fidelity at the molecular level.

2.3.3 Functional Validation

Functional validation is an important step to tell whether a biomimetic nasal mucosa organoid model has real physiological functions. In nasal mucosa organoids, mucociliary clearance is a key indicator. It is usually assessed by recording ciliary beating frequency and coordination using high-speed video microscopy [65]. Clearance ability can also be measured quantitatively by tracking the movement of fluorescent microspheres inside the organoid lumen [66]. Epithelial barrier function is another key parameter to evaluate whether nasal mucosa organoids mimic the normal physiological state of nasal mucosa [67]. However, to measure transepithelial electrical resistance (TEER), the organoid-derived cells usually need to be grown in a Transwell system or a microfluidic chip, so that electrodes can touch both the top (apical) and bottom (basolateral) sides [68]. In addition, permeability tests using tracer molecules such as FITC-dextran can be used to directly see how well the barrier blocks large molecules. For olfactory organoid models, assessing neural functional maturity requires more specialized methods [69]. For example, calcium imaging can detect sensory neuron responses to odorant stimulation, or patch-clamp recording can measure action potentials to check olfactory signal transmission [70].



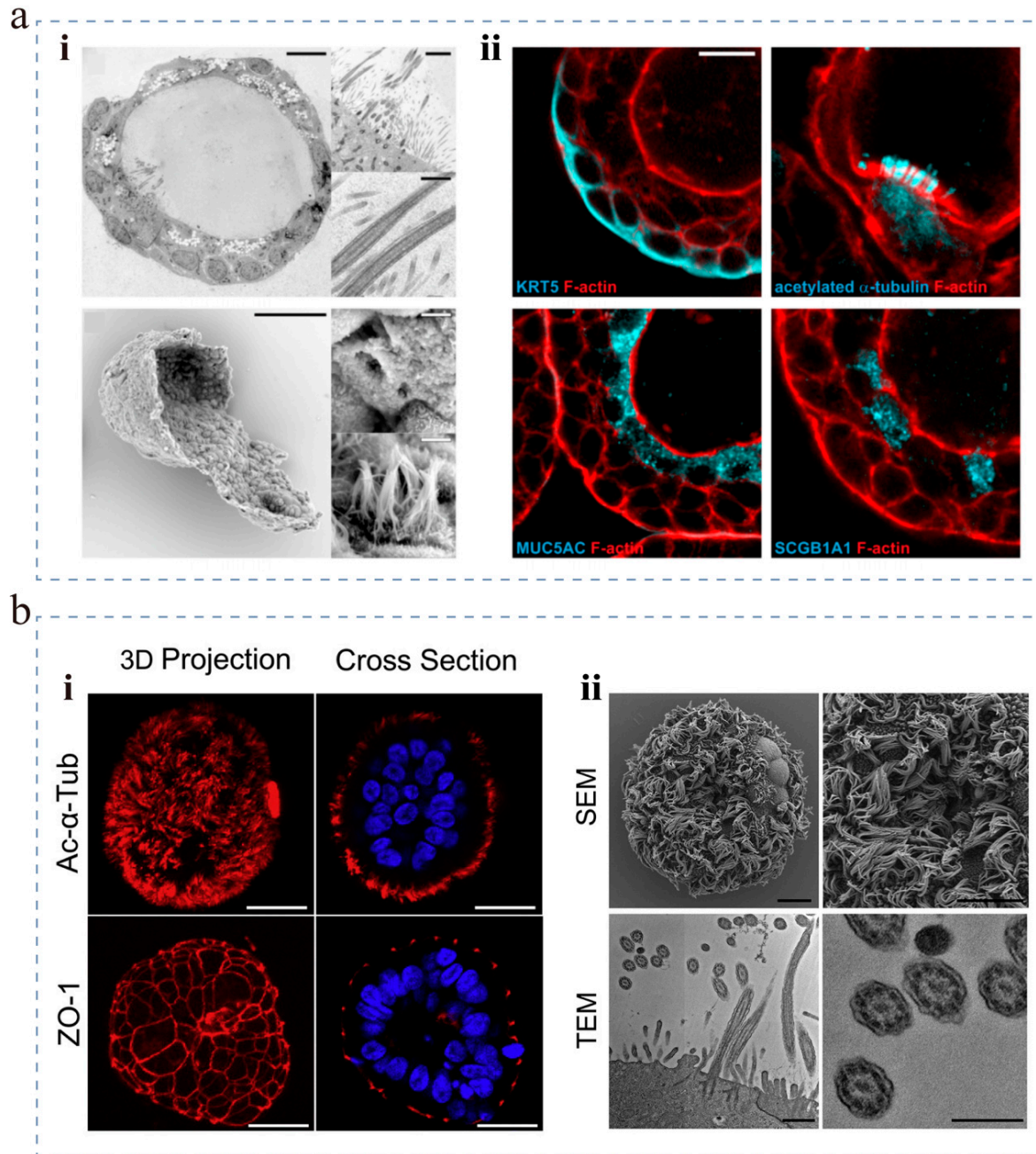


Figure 6: Morphological and marker characterization of airway organoids. **(a)** **(i)** TEM and SEM images showing ultrastructural features and cilia (scale bars: TEM, 10 μ m, 2 μ m, and 500 nm; SEM, 50 μ m and 2 μ m). **(ii)** Immunofluorescence staining of cell type markers, including basal cells (KRT5), ciliated cells (acetylated α -tubulin), and secretory cells (MUC5AC, SCGB1A1), with F-actin labeling the cytoskeleton (scale bar, 10 μ m) [61]. Copyright 2019, the authors. **(b)** **(i)** Immunofluorescence shows the ciliated cell marker Ac- α -Tub and the tight junction protein ZO-1 (scale bars, 25 μ m). **(ii)** SEM and TEM images showing the surface cilia and ultrastructure (scale bars: SEM, 10 μ m; TEM, 800 nm (left) and 400 nm (right)) [62]. Copyright 2022, the authors.

3 Strategies for Constructing Complex Bionic Nasal Mucosa from Simple Organoids

Although conventional nasal mucosa organoid systems have successfully recapitulated certain aspects of the epithelial three-dimensional architecture and fundamental functions, they still face substantial limitations regarding cellular diversity, spatial tissue hierarchy, and dynamic microenvironmental simulation. To achieve higher fidelity tissue biomimicry, researchers have progressively introduced multicellular co-culture systems, advanced bioengineering technologies, and microfluidic culture platforms [71]. These innovations facilitate the transition of nasal mucosa models from simple epithelial spheres to complex bionic tissue constructs [72,73]. This section systematically summarizes three major validated construction strategies that represent the core directions for developing advanced nasal mucosa models.

3.1 Complexification of Cellular Composition

The nasal mucosa *in vivo* is a highly heterogeneous multicellular system composed of epithelial cells, fibroblasts, immune populations, neuron cells, and perivascular components [74]. Through direct cell–cell contact and paracrine signaling, these diverse populations cooperate to maintain mucosal homeostasis and orchestrate stress responses [75]. Early models were predominantly epithelial-centric, lacking essential stromal and immune constituents, which restricted their utility in studying complex processes such as chronic inflammation, barrier repair, and neuroregeneration [76].

Fibroblasts were among the first non-epithelial components incorporated into these systems [77]. By secreting extracellular matrix components including collagen and laminin, alongside paracrine factors such as Fibroblast Growth Factor, Hepatocyte Growth Factor, and Transforming Growth Factor-beta, fibroblasts significantly promote epithelial polarization and differentiation [78]. Within co-culture systems, their presence enhances structural integrity and stabilizes the proportion of secretory goblet cells. Multiple studies have confirmed that introducing well-characterized stromal cells, such as primary nasal fibroblasts or mesenchymal stem cells, substantially improves tissue stability and physiological fidelity [79].

Furthermore, as an important immunological barrier, the nasal mucosa harbors innate immune cells including macrophages, dendritic cells, and innate lymphoid cells, which play pivotal roles in allergic inflammation and viral defense [80]. Current research primarily focuses on two strategies: short-term co-culture with immune cells differentiated from peripheral blood mononuclear cells to reconstruct early immune responses, and the stimulation of epithelial cells with cytokines such as Interleukin-4 and Interleukin-13 to induce immune related activation [81,82]. Emerging evidence suggests that organoids can exhibit reversible responses to inflammatory mediators including Tumor Necrosis Factor-alpha and Interleukin-6, providing a novel platform for investigating immune dysregulation [83,84]. In the olfactory mucosa, the coexistence of olfactory sensory neurons and supporting cells is crucial for sensory perception [85,86]. Recent findings demonstrate that maintaining populations of basal and supporting cells within olfactory epithelial organoids can successfully induce the differentiation of neuron-like cells that express synaptic markers and display calcium signaling responsiveness [87,88].

3.2 Integration with Microfluidic Technology

3.2.1 Perfusion-Based Microfluidic Chips

In traditional static three-dimensional culture systems, the exchange of nutrients and metabolites depends solely on passive diffusion, which fails to reproduce the continuous airflow, fluid shear stress, and chemical gradients present in the nasal cavity. Microfluidic technology provides a controllable and reproducible engineering solution to these limitations. Microfluidic chips, through precisely designed

microchannels and pump controlled systems, enable the dynamic regulation of fluid velocity, shear stress, and solute gradients. As an example, Koch et al. established a biomimetic nasal mucosa-on-chip platform featuring distinct apical airflow and basal medium compartments separated by a porous membrane, allowing regulated bidirectional airflow to mimic physiological conditions (Fig. 7a,e) [89].

In nasal mucosa research, embedding organoids within microfluidic chambers for continuous perfusion culture markedly improves oxygen and nutrient supply while minimizing metabolite accumulation, thereby extending viability and functional stability [90,91]. Importantly, microfluidic platforms can simulate dynamic exposure to external stimuli [92]. By periodically introducing allergens, viral particles, or inflammatory mediators, researchers can reconstruct physiologically relevant stimulation patterns that mimic natural exposure [93]. Unlike static treatments, such dynamic exposures reveal time-dependent changes in epithelial barrier disruption and repair processes [94]. Evidence from airway organ-on-chip studies suggests that perfusion-based dynamic culture promotes airway epithelial differentiation and mucociliary maturation, with barrier integrity assessable by TEER and ciliary activity measurable by ciliary beat frequency [41,95]. Furthermore, combining air–liquid interface configurations with microfluidic systems allows for a more accurate recreation of air-exposed epithelial surfaces, enabling sophisticated studies on inhaled pathogen infection and aerosol toxicology [96]. Walls et al. developed a nasal airway-on-chip model consisting of an air channel and a basal medium chamber separated by a porous membrane. The system was designed to mimic bidirectional airflow during normal breathing and to investigate how different airflow conditions affect epithelial cell differentiation and maturation (Fig. 7b) [97].

3.2.2 Microfluidic Microcapsule Mediated Organoid Tissue Engineering

Besides perfusion-based microfluidic chips, microfluidic electrospray and microcapsule technologies also provide another engineering strategy for building controllable organoid microenvironments [98]. Wang et al. used a microfluidic electrospray microcapsule platform to construct biomimetic vascularized liver organoids. In this system, hiPSC-derived hepatocytes were encapsulated in a carboxymethyl cellulose core. Sodium alginate and hyaluronic acid methacryloyl formed a composite hydrogel shell. This allowed the formation of size-controllable core–shell microcapsules and subsequent organoid assembly (Fig. 8a) [99]. Fluorescence staining showed that cell viability and proliferation were maintained (Fig. 8b(i)) [99]. SEM images showed the internal structure and surface morphology of the microcapsule shell (Fig. 8b(ii)) [99]. Although this study was performed in liver regeneration and did not directly focus on nasal mucosa organoids, it shows how microfluidic microcapsules can control organoid size, hydrogel structure, cell spatial compartmentalization, and vascular cell integration. These engineering principles may be applied to the future construction of bionic nasal mucosa organoids.

Similarly, microfluidic systems can also be used for the spatial assembly of different organoid types. Zhu et al. encapsulated hiPSCs into microcapsules by microfluidic electrospray. They then induced them into region-specific brain organoids and assembled them in a multilayered microfluidic chip. In this way, they constructed human brain assembloids (Fig. 8c(i)) [100]. The chip consisted of a micropillar array and a complementary microhole array. This design allowed microcapsules carrying different organoids to be arranged in a preset order. Fluorescence imaging showed that organoids labeled with different colors could be arranged in a controlled way. These organoids could also fuse later to form patterned brain assembloids (Fig. 8c(ii)) [100]. This strategy shows that microfluidics can be used not only for organoid generation, but also for the spatial assembly of multicellular and multi-organoid structures.

In another example, Zhi et al. used microfluidic electrospray technology to construct self-organized vascularized liver organoids in hydrogel microcapsules. This formed size-controllable self-organized vascularized liver organoids with three-dimensional structures (Fig. 8d(i)) [101]. Bright-field images showed that the organoids grew well inside the microcapsules (Fig. 8d(ii)) [101]. Fluorescence and SEM images further confirmed the core-shell structure and surface morphology of the microcapsules (Fig. 8d(iii,iv)) [101]. Confocal imaging showed that HUVECs were distributed inside the organoid structures. This suggests vascular cell integration and the formation of self-organized vascular networks (Fig. 8d(v)) [101]. Although these studies were conducted in brain and liver organoid systems rather than nasal mucosa, the underlying principles are transferable to the construction of bionic nasal mucosa organoids. Specifically, microfluidic microcapsules provide controllable three-dimensional microenvironments for regulating organoid size and spatial organization and for incorporating vascular or stromal cells, while microfluidic guided assembly enables the patterned organization of distinct cellular or tissue components. These strategies may help address current limitations of nasal mucosa organoids in cellular complexity, spatial organization, and vascularization, thereby providing useful engineering references for constructing more physiologically relevant bionic nasal mucosa models.

3.3 Integration with Organ-on-a-Chip Technology

Building upon microfluidic foundations, organ-on-a-chip technology represents an advanced biomimetic platform designed to recreate spatial tissue compartmentalization and mechanical microenvironments within a single device [90]. Integrating nasal mucosa organoids with organ-on-a-chip systems is a pivotal strategy for overcoming the limitations of conventional organoids in spatial organization [102].

A typical nasal mucosa-on-chip design consists of two interacting but physically separated microenvironments: an apical chamber representing the air-exposed epithelial surface and a basal chamber mimicking the vascular or stromal interface. For example, Gholizadeh et al. developed a dual-channel human nasal epithelial mucosa-on-a-chip in which nasal epithelial cells were cultured at an air-liquid interface on a permeable membrane, allowing aerosolized nasal formulations to be deposited through the upper channel and drug transport to be monitored in real time through the basal channel (Fig. 7c,d) [97].

The introduction of an air-liquid interface allows the epithelial layer to be directly exposed to air while receiving nutrients from the basal side. This setup is important for maintaining ciliary movement and mucus secretion. In addition, these platforms can apply mechanical stimuli, such as cyclic pressure changes and airflow-induced shear stress, to mimic the dynamic conditions that occur during normal breathing [103]. Using a human airway lung-on-chip model, Nawroth et al. found that breathing-like mechanical stimuli, including dynamic medium flow, airflow, and cyclic stretch, accelerated mucociliary maturation of primary human airway epithelial cells, promoted polarized mucociliary clearance, and changed the composition of specific epithelial cell types [41]. These findings indicate that mechanical forces are crucial for the regulation of airway epithelial differentiation and maturation.

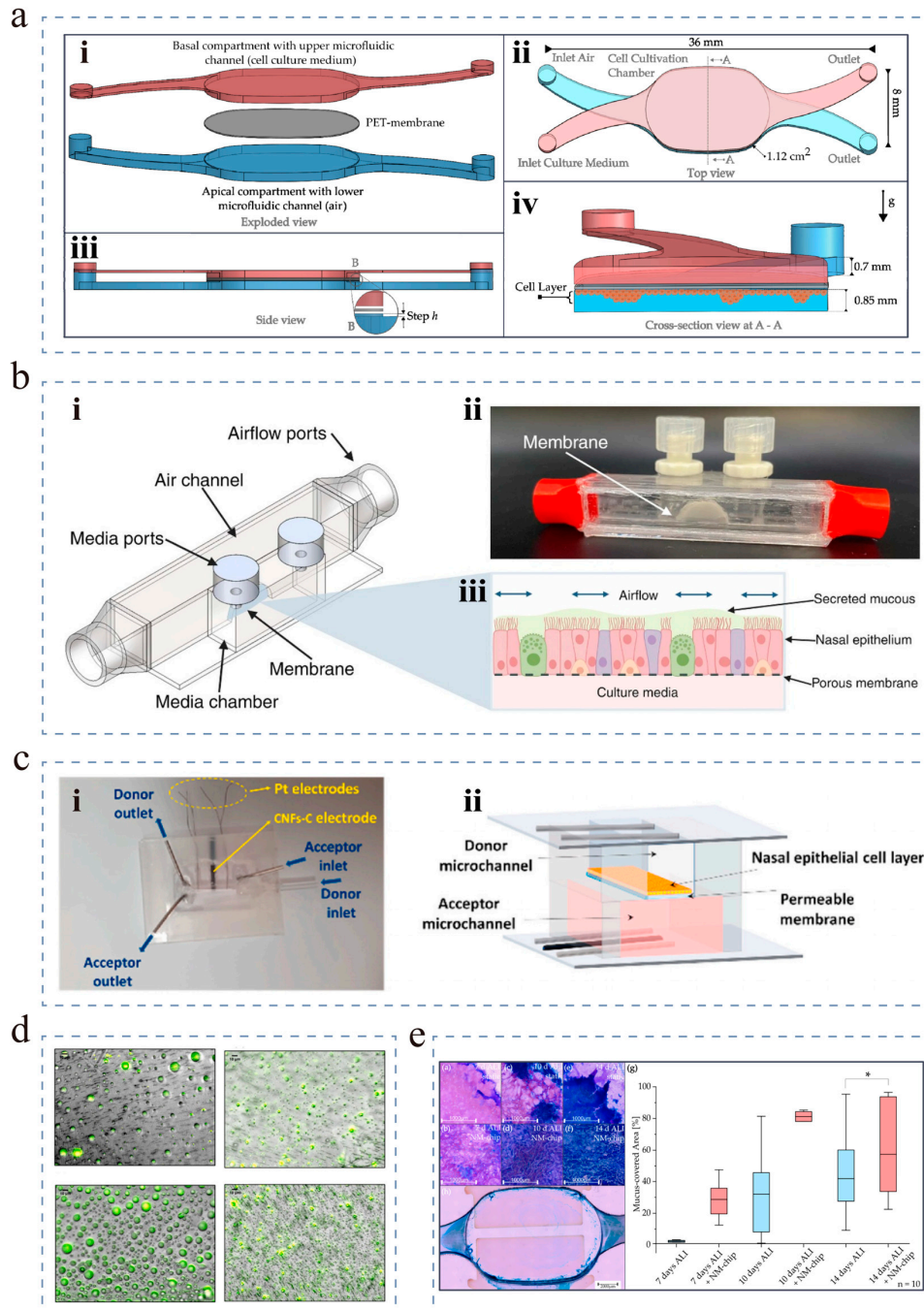


Figure 7: Representative microfluidic strategies for constructing organoid-based bionic nasal mucosa models. **(a)** Microfluidic nasal mucosa chip for dynamic airflow culture. **(i)** Exploded view of the chip structure with culture medium and air channels separated by a porous membrane. **(ii)** Top view showing the air inlet/outlet and central cell culture chamber. **(iii)** Side view of the chip architecture. **(iv)** Cross-sectional view showing epithelial cell culture under airflow stimulation [89]. Copyright 2023, the authors. **(b)** Nasal airway-on-chip model. **(i)** Schematic design showing airflow ports, media ports, air channel, media chamber, and membrane. **(ii)** Photograph of the assembled chip. **(iii)** Schematic organization of differentiated nasal epithelium on a porous membrane under airflow [97]. Copyright 2024, IOP Publishing Limited. **(c)** Microfluidic nasal epithelial mucosa-on-a-chip model. **(i)** Device structure showing the donor and acceptor channel inlets/outlets; **(ii)** Cross-sectional schematic showing ALI culture of nasal epithelial cells on a

permeable membrane [97]. Copyright 2022, Elsevier B.V. All rights reserved. (d) Representative microscopic images showing aerosol deposition in the chip under different airflow and formulation conditions [97]. Copyright 2022, Elsevier B.V. All rights reserved. (e) Short-term dynamic airflow stimulation significantly promotes mucus production and improves its spatial distribution homogeneity in a nasal mucosa-on-chip model ((g) Quantification of the mucus-covered area under static air-liquid interface culture and dynamic nasal mucosa-on-chip culture conditions (* indicates $p < 0.05$). (h) Alcian blue staining of mucus in the apical compartment of the nasal mucosa-on-chip model after 7 days of air-liquid interface culture followed by dynamic cultivation [89]). Copyright 2023, the authors.

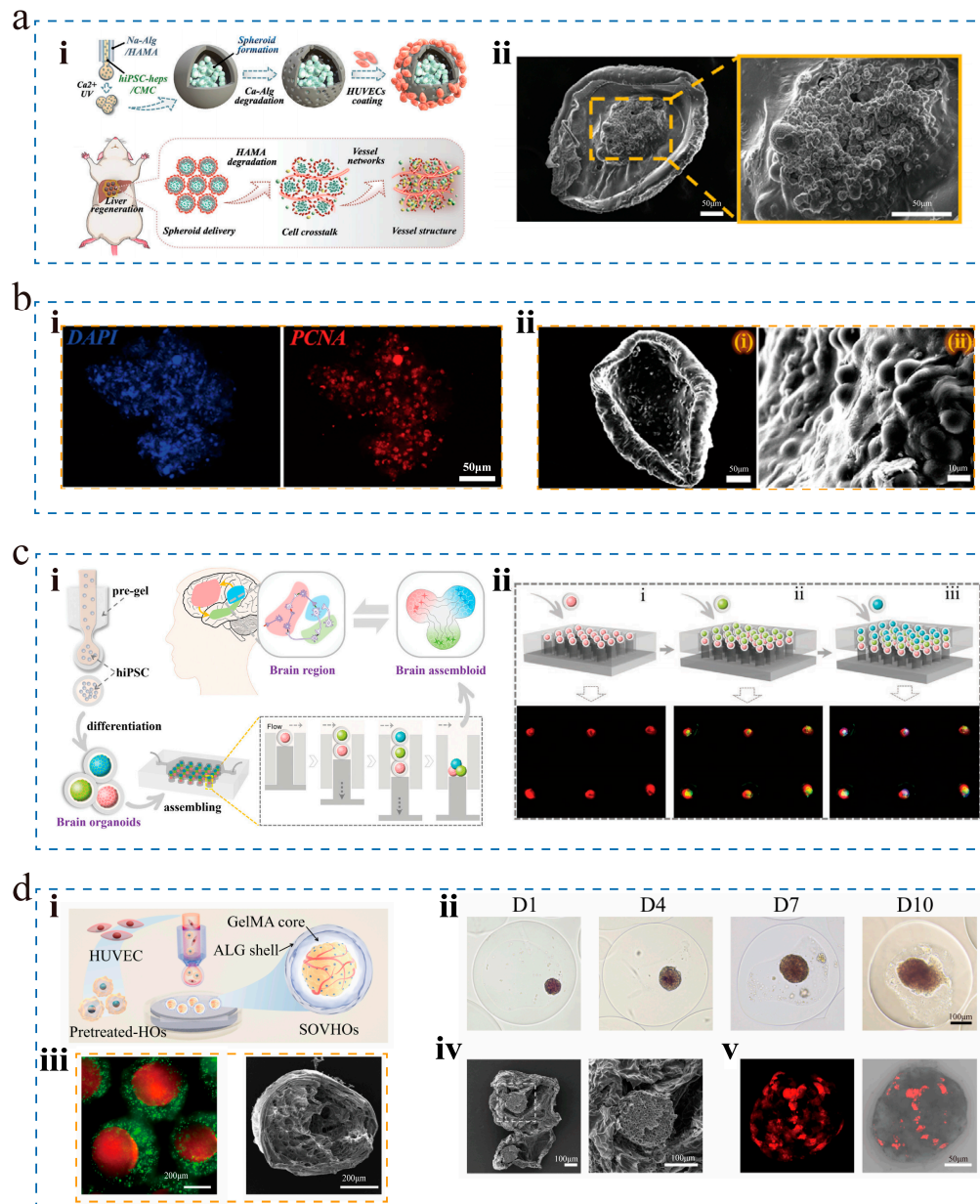


Figure 8: Microfluidics-based strategies for organoid fabrication. (a) Generation of biomimetic microcapsules. (i) Schematic illustration of the microfluidic fabrication process for microencapsulated organoids and their application. (ii) SEM images showing the microcapsules with encapsulated organoids and their magnified internal details [99].

Copyright 2024, the authors. **(b)** Characterization of microcapsules and organoids. **(i)** Fluorescence images (DAPI in blue, PCNA in red) demonstrating the proliferative capacity of cells within the encapsulated spheroids. **(ii)** SEM images detailing the interior porous structure (**left**) and surface topography (**right**) of the microcapsule shell [99]. Copyright 2024, the authors. **(c)** Microfluidic chip-assisted organoid assembly. **(i)** Schematic diagram of assembling region-specific brain organoids into complex assembloids using dynamic microfluidic flow. **(ii)** Fluorescence images demonstrating the precise patterned arraying and fusion of multi-colored organoid microcapsules on the chip [100]. Copyright, 2023 Wiley-VCH GmbH. **(d)** Culture and characterization of organoids within microfluidic microcapsules. **(i)** Schematic illustration of the construction of organoid microcapsules based on a core-shell structure. **(ii)** Bright-field images showing the growth and morphological changes of organoids within the microcapsules. **(iii)** Fluorescence and SEM images characterizing the core-shell structure of the microcapsules. **(iv)** SEM images showing the morphology of the organoids. **(v)** Confocal fluorescence images showing the cellular distribution within the microcapsules, with HUVECs in red [101]. Copyright 2025, the authors.

4 Applications of Bionic Nasal Mucosa Organoid Models

The core value of bionic nasal mucosa organoid models lies in their ability to simultaneously reconstruct the cellular heterogeneity of pseudostratified epithelium, establish clear apicobasal polarity, and develop highly specialized apical structures [35]. These features, including motile cilia, microvilli, and functional mucus layers, make them a unique platform for studying mucosal homeostasis, mucociliary clearance, and pathogen-host interactions [104]. Such complex dynamics are often difficult to achieve or analyze in traditional two-dimensional monolayer cultures. In the following sections, we provide a systematic overview of their key applications in fundamental biological research, disease modeling, and infection studies as summarized in Fig. 9.

4.1 Fundamental Biological Research

In recent years, nasal and airway epithelial organoid models have revealed that apical epithelial structures actively participate in respiratory viral infection rather than serving only as passive barriers [105]. In reconstructed human bronchial epithelium, Robinot et al. showed that SARS-CoV-2 preferentially infects ciliated epithelial cells and induces progressive loss of the ciliary layer, as evidenced by reduced β -tubulin staining, decreased β -tubulin-positive areas, and deciliated epithelial regions observed after infection (Fig. 10a) [106]. Similarly, Sano et al. used bronchial organoid-derived air-liquid interface (BO-ALI) cultures to demonstrate that SARS-CoV-2 efficiently infects acetylated α -tubulin-positive ciliated cells, whereas KRT5-positive basal cells largely survive infection and contribute to epithelial repair. Notably, surviving basal cells differentiated into acetylated α -tubulin-positive ciliated cells by day 15, and this regenerative process was impaired when FGF10 was removed from the differentiation medium (Fig. 10b) [107]. These findings suggest that organoid-derived airway epithelial models can capture both virus-induced ciliary injury and subsequent epithelial regeneration.

Additionally, Wu et al. further clarified how SARS-CoV-2 breaches the mucociliary barrier in primary nasal epithelial organoid cultures. They showed that removal of mucin barriers by StcE increased viral infection, while SEM and TEM analyses revealed viral particles attached to motile cilia during the early stage of infection (Fig. 10c) [104]. Mechanistically, SARS-CoV-2 was proposed to use motile cilia to traverse the mucus layer and subsequently exploit microvillar remodeling for viral egress and dissemination, a process involving cytoskeleton-related signaling pathways, particularly p21-activated kinases [104]. Together, these findings indicate that cilia, mucus-associated structures, and microvilli are active regulators of viral entry, spread, and epithelial repair dynamics.

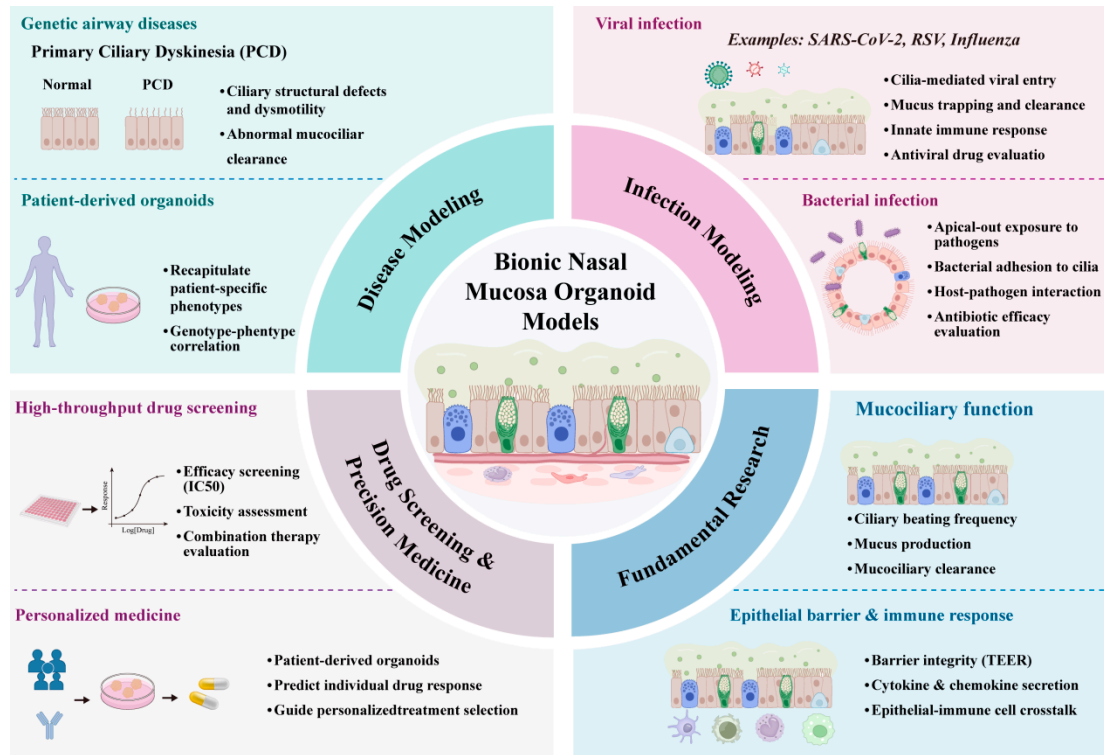


Figure 9: Applications of bionic nasal mucosa organoid in basic research, disease modeling, infection studies, drug screening, and personalized medicine.

Beyond virology, nasal organoids serve as a platform for exploring epithelial homeostasis and differentiation plasticity. Dreyer et al. established a submerged differentiation model using human nasal epithelial cells obtained through minimally invasive nasal brushings. By targeting Notch and BMP signaling with small-molecule inhibitors such as DAPT and DMH1, they induced these cells to form differentiated epithelial cultures containing basal, secretory, and ciliated populations, even under submerged culture conditions [108]. This suggests that modulation of key developmental signaling pathways can partially compensate for the absence of conventional air-liquid interface culture and provides a platform for studying nasal epithelial differentiation and disease-relevant phenotypes.

4.2 Disease Modeling

Nasal organoids excel in disease modeling due to the feasibility of patient-derived studies and the reproducibility of functional phenotypes. Compared to lower airway samples, nasal biopsies are minimally invasive and can be repeatedly obtained, providing an ideal starting point for personalized research [109,110].

4.2.1 Patient-Derived Organoids for Genetic and Chronic Airway Diseases

Patient-derived nasal organoids provide a valuable system for modeling monogenic and chronic airway diseases, particularly those involving epithelial transport or ciliary dysfunction. In models of primary ciliary dyskinesia, patient-derived organoids stably recapitulate disease-associated phenotypes, including reduced ciliary density, structural abnormalities, and decreased ciliary beating frequency. Importantly, these phenotypes are maintained after extensive expansion, allowing genotype-dependent differences in ciliary assembly and function to be investigated across different genetic backgrounds [111].

In cystic fibrosis research, nasal organoids have shown strong translational potential. In submerged differentiation systems, nasal epithelial cells can form cystic organoid structures within 48 h after embedding in extracellular matrix. Functionally, forskolin-induced swelling assays demonstrate that organoids derived from cystic fibrosis patients show markedly reduced swelling compared with healthy controls, directly reflecting impaired CFTR-mediated ion and fluid transport. Moreover, organoids carrying different CFTR genotypes display distinct responses to modulator combinations, including VX-809, VX-770, and VX-661, and these responses correlate with clinical outcomes [112,113]. Thus, patient-derived nasal organoids provide a high-fidelity platform for quantifying CFTR function and predicting individualized therapeutic responses.

4.2.2 Organoid Models for Respiratory Infectious Diseases

Respiratory infectious disease modeling represents another major application of nasal and airway organoids, as the nasal cavity and proximal airway are often the initial sites of pathogen entry and replication [114]. In viral infection studies, nasal and airway epithelial organoid systems have been used to model SARS-CoV-2 and RSV infection under conditions that preserve epithelial polarity, mucociliary differentiation, and apical barrier structures [106,107,114]. These models allow researchers to evaluate not only viral replication, but also how viruses interact with the mucociliary barrier, exploit ciliary or microvillar dynamics, and induce epithelial damage and repair. In this context, Chiu et al. established optimized 2D airway organoids and showed that the Omicron variant exhibited higher infectivity and replicative fitness than an ancestral WT strain, as demonstrated by NP and acetylated α -tubulin staining, flow cytometric analysis of dsRNA and ACTUB-positive cells, and increased viral genome copies and TCID₅₀ titers (Fig. 10d) [115]. These results illustrate the utility of airway organoid platforms for comparing variant-specific infectivity, quantifying viral replication, and evaluating host epithelial responses in a physiologically relevant setting.

Bacterial infection modeling further highlights the importance of organoid polarity [116]. A major limitation of conventional basal-out organoids is that their apical surface is enclosed within the internal lumen, restricting access of bacterial pathogens such as *Pseudomonas aeruginosa* to physiologically relevant apical receptors [117]. Although mechanical disruption or microinjection can provide pathogen access, these approaches may compromise tissue integrity or limit experimental throughput. In contrast, suspension culture can induce polarity reversal and generate apical-out organoids with externally exposed cilia and mucus-producing surfaces [118]. When combined with mucociliary differentiation, this strategy enables controlled bacterial inoculation under submerged conditions, quantitative assessment of infection-associated changes in ciliary motility, and evaluation of therapeutic interventions [119]. Therefore, polarity engineering, especially the establishment of reliable apical access, is essential for improving the physiological relevance of bacterial infection models.

Overall, nasal organoids integrate patient-specific genetic background, epithelial architecture, apical-basal polarity, and functional phenotypes within a single experimental platform. These features make them particularly valuable for modeling both inherited airway disorders and respiratory infections, thereby providing a critical bridge between mechanistic research and clinical translation.

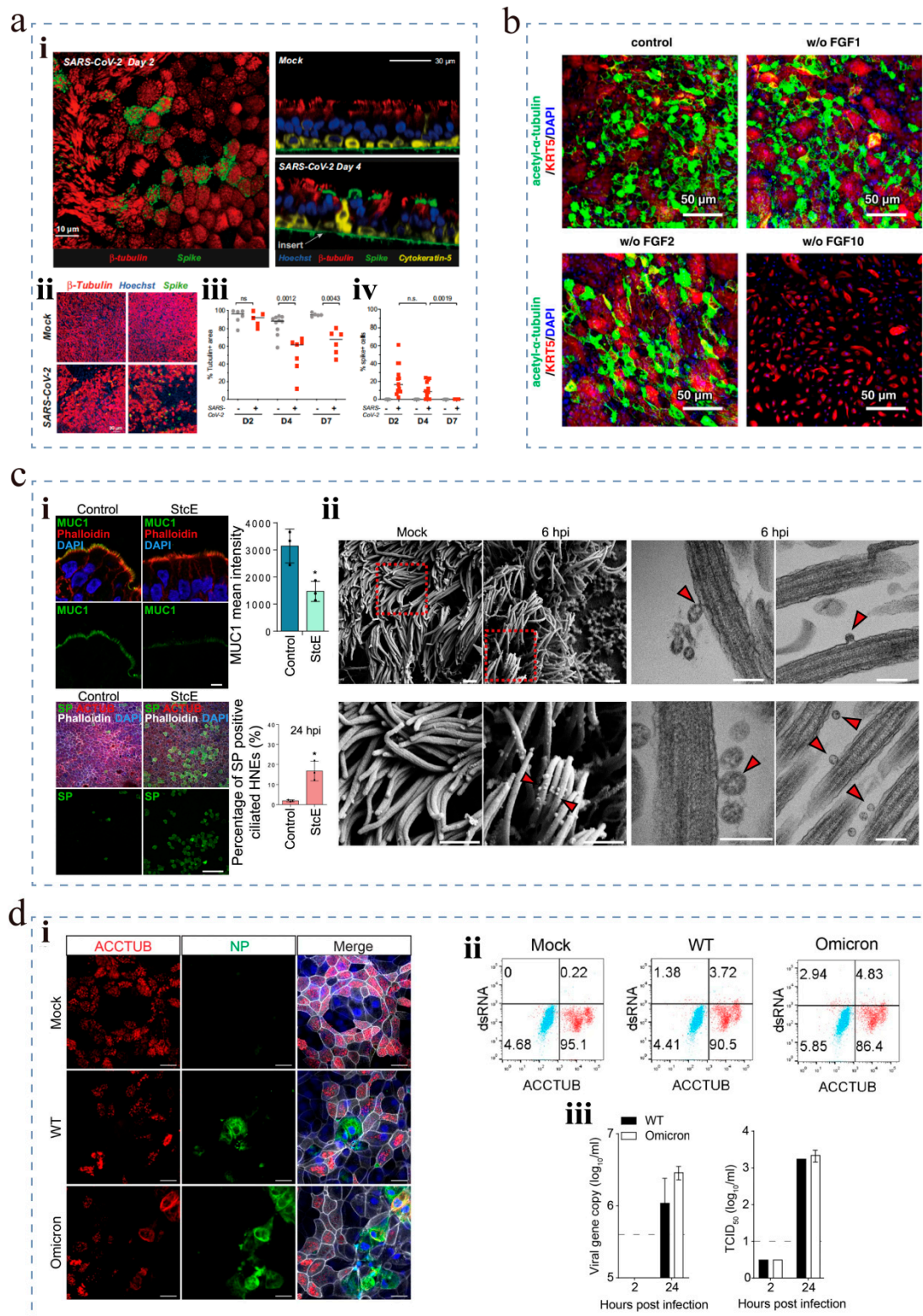


Figure 10: Airway organoids for disease modeling. (a) SARS-CoV-2 targets ciliated cells and damages the ciliary layer. (i) Confocal images of SARS-CoV-2-infected epithelium. (ii) β -tubulin staining in mock and infected epithelia. (iii) Quantification of β -tubulin-positive area. (iv) Quantification of spike-positive cells [106]. Copyright 2021, the

authors. **(b)** Immunofluorescence staining of acetylated α -tubulin and KRT5 at day 15 after SARS-CoV-2 infection [107]. Copyright 2022, the authors. **(c)** SARS-CoV-2 targets ciliated nasal epithelial cells during early infection. **(i)** Mucin removal increases infection (* indicates $p < 0.05$; scale bars, 5 μm (upper images) and 50 μm (lower images)). **(ii)** SEM and TEM images show that cilia are an early site of viral attachment (scale bars: SEM, 1 μm ; TEM, 200 nm). Red dashed boxes indicate magnified regions, and red arrowheads indicate viral particles [104]. Copyright 2022, the authors. **(d)** WT and Omicron infection in airway organoids. **(i)** NP and ACTUB staining at 24 hpi (scale bar, 20 μm). **(ii)** Flow cytometry of dsRNA and ACTUB. **(iii)** Viral load and TCID₅₀ assay [115]. Copyright 2022, the authors.

5 Conclusion and Outlook

With the deepening understanding of nasal mucosal physiology and the rapid evolution of bioengineering, the development of *in vitro* nasal models is no longer limited to traditional 2D cell cultures or animal models. More and more high-fidelity bionic nasal mucosa organoids have been proposed and applied to respiratory research [120]. In this review, we have systematically summarized the principles of cultivating nasal mucosa organoids from different stem cell sources, as well as the key identification methods for their morphological and functional validation [35]. To overcome the limitations of simple epithelial organoids, advanced strategies such as multicellular co-culture, microfluidics, and organ-on-a-chip technologies have been integrated to reconstruct the complex physiological microenvironment of the nasal cavity [121]. These bionic models provide powerful platforms for studying fundamental biology, disease modeling (e.g., PCD, CF, and viral/bacterial infections), and personalized drug screening. However, despite these remarkable achievements, several challenges remain in practical applications and clinical translation.

Firstly, while adult stem cell derived organoids excel in reflecting patient-specific phenotypes, and (PSC)-derived models offer unparalleled advantages in studying embryonic development and genetic diseases, the long-term stability and standardization of these cultures require further optimization. Current cultivation systems still rely heavily on animal-derived matrices like Matrigel, which introduces batch-to-batch variability and limits clinical applications in regenerative medicine [34,122]. The development of defined, tunable synthetic hydrogels or recombinant protein scaffolds remains a critical direction to improve experimental reproducibility and safety. Secondly, although current bionic nasal mucosa models can recapitulate the pseudostratified epithelial architecture and mucociliary clearance functions, they often lack essential “non-epithelial” components. The natural nasal mucosa is a highly integrated system containing vascular networks, innate immune cells (such as macrophages and dendritic cells), and sensory nerve endings. Future research should focus on the “complexification” of cellular composition—specifically, integrating vascularization to provide nutrient exchange and incorporating immune cells to simulate early inflammatory responses and host-pathogen interactions more accurately [123]. Thirdly, the convergence of organoid technology with organ-on-a-chip and microfluidic platforms represents a paradigm shift. While we have summarized how these hybrid systems simulate dynamic airflow, fluid shear stress, and air-liquid interfaces, most current “nasal-on-a-chip” models are still in the laboratory stage. Enhancing the throughput of these systems and integrating real-time biosensors (for monitoring TEER, pH, or cytokine release) will be crucial for large-scale drug toxicity testing and rapid viral neutralization assays, as demonstrated in recent studies on SARS-CoV-2 and RSV [93]. Last but not least, the polarity engineering of organoids such as the generation of “apical-out” structures has effectively addressed the technical bottleneck of “apical accessibility” in bacterial and viral infection modeling. However, the regulatory strategies within these graded bionic constructs, such as the use of specific signaling modulators (Notch or BMP inhibitors) to balance ciliary vs. goblet cell differentiation, are expected to be combined with 3D bioprinting [117]. This

will enable the precise spatial assembly of cells and scaffolds to create more powerful, anatomically accurate biomimetic nasal substitutes.

Importantly, integrating nasal mucosa organoids with microfluidic and organ-on-a-chip technologies may further enhance their translational potential by providing physiologically relevant platforms for disease modeling and drug screening. In particular, combining these technologies with patient-derived organoids may facilitate individualized assessment of disease phenotypes and therapeutic responses, thereby supporting future personalized medicine applications. In general, although organoid-based bionic nasal mucosa has made significant strides in bridging the gap between basic science and clinical application, there is still a long way to go toward a fully “total bionic” system. We hope that this review will help researchers understand the current state of nasal organoid engineering and provide inspiration for the multidisciplinary convergence of biology, materials science, and micro-nanotechnology to develop more efficient respiratory disease models and therapeutic strategies.

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