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Regenerative and Stem-Cell Based Approaches for Rhinitis: From Pathophysiology to Translational Models

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ABSTRACT

Rhinitis, a prevalent inflammatory condition of the upper airway, imposes a substantial global health burden. While current pharmacotherapies alleviate symptoms, they are ineffective in restoring epithelial barrier integrity or reversing structural damage, underscoring a critical therapeutic gap. This review explores the potential of regenerative medicine and stem cell-based strategies to address these limitations. We first explain the pathophysiological mechanisms across rhinitis subtypes and evaluate the constraints of existing management options. The application of advanced *in vitro* models and nasal organoids for dissecting disease mechanisms and screening candidate therapeutics is then examined. Furthermore, we highlight the promise of mesenchymal stem cells (MSCs) and tissue engineering approaches in rhinitis management. Preclinical evidence demonstrates that MSCs can mitigate nasal inflammation, reduce eosinophilic infiltration, and promote mucosal repair through their paracrine actions and immunomodulatory capacities, which include restoring the Th1/Th2 balance and enhancing epithelial barrier function. The integration of these biologic and bioengineering approaches heralds a paradigm shift from symptomatic control towards durable tissue restoration and immune rebalancing in rhinitis therapy.

1. INTRODUCTION

Rhinitis is one of the most prevalent inflammatory conditions of the upper airway, characterized by nasal congestion, rhinorrhoea, sneezing, and itching. In allergic rhinitis, ocular symptoms such as tearing and conjunctival irritation often accompany nasal complaints. Though often dismissed as a benign nuisance, rhinitis imposes a substantial global burden, impairing quality of life, sleep, cognition, and productivity. In children, it contributes to learning difficulties and behavioral disturbances. Importantly, rhinitis frequently coexists with asthma, chronic rhinosinusitis, and otitis media, amplifying morbidity. Health economic analyses estimate billions of dollars in lost productivity and healthcare costs worldwide [1]. These realities highlight the urgent need for improved therapeutic strategies.

2. CLASSIFICATION AND EPIDEMIOLOGY

Rhinitis is traditionally categorized into allergic, nonallergic, infectious, and mixed subtypes. Allergic rhinitis (AR) is an IgE-mediated hypersensitivity reaction to environmental allergens, further subdivided into seasonal allergic rhinitis (SAR), triggered by pollens, and perennial allergic rhinitis (PAR), caused by year-round allergens such as dust mites and pet dander. Nonallergic rhinitis (NAR) encompasses syndromes triggered by irritants (pollution, smoke), abrupt weather changes, hormonal fluctuations, or medications. Infectious rhinitis is most frequently viral, though bacterial or fungal pathogens can contribute. Mixed rhinitis reflects overlapping allergic and nonallergic mechanisms [2].

Epidemiological studies estimate that AR affects 10% - 30% of the global population, with prevalence especially high in industrialized and urbanizing regions [3]. Although mortality is low, the chronicity of symptoms and their interference with daily life impose a heavy burden. The “united airway disease” concept highlights the continuum between rhinitis and asthma, whereby managing rhinitis can improve asthma outcomes [4]. Environmental factors, including air pollution, climate change, and lifestyle changes such as diet and microbiome alterations, also play significant roles in rising prevalence.

3. PATHOPHYSIOLOGY AND MECHANISMS

In AR, allergen sensitization drives IgE production under the influence of T helper 2 (Th2) lymphocytes. IgE binds FcεRI receptors on mast cells and basophils. Re-exposure to allergens triggers mast cell degranulation and mediator release, causing acute symptoms. A late-phase response follows, involving eosinophils, Th2 cells, and type 2 innate lymphoid cells (ILC2s), sustained by cytokines such as IL-4, IL-5, and IL-13. Epithelial-derived alarmins (TSLP, IL-25, IL-33) amplify Th2 polarization [5].

In NAR, mechanisms are more heterogeneous, including neurogenic inflammation via substance P and CGRP, autonomic imbalance, hormonal influences, and medication-induced effects. Infectious rhinitis arises from viral replication and epithelial destruction. Across all subtypes, epithelial barrier dysfunction and impaired mucociliary clearance play central roles. Dysbiosis of the nasal microbiota has also been implicated [6]. In nonallergic (vasomotor) rhinitis, neurogenic inflammation—mediated by trigeminal sensory neuropeptides (e.g., substance P, CGRP)—contributes to hypersecretion and congestion; capsaicin desensitization trials support a neural driver. Regenerative strategies that restore epithelial barrier integrity and recalibrate neuro-epithelial crosstalk may therefore benefit selected NAR endotypes.

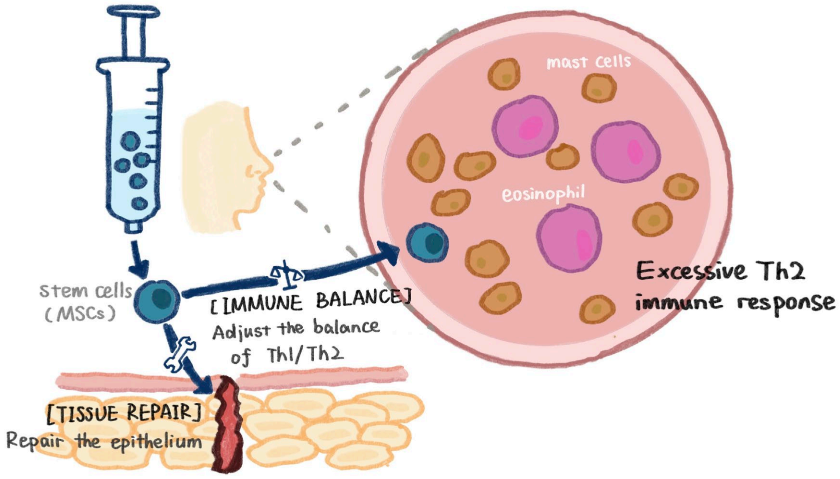

Figure 1. **Mechanism of stem cell therapy in rhinitis.**

Emerging research links epithelial dysfunction in rhinitis to genetic and epigenetic alterations in barrier-related proteins such as filaggrin, claudins, and occludins. Furthermore, chronic inflammation leads to tissue remodeling, basement membrane thickening, and goblet cell hyperplasia, perpetuating the disease [7]. Understanding these mechanisms provides a rationale for regenerative approaches aimed at restoring mucosal structure and function.

Microbiome-barrier interactions: Nasal microbial dysbiosis correlates with AR severity, and multi-omics studies implicate disturbed epithelial-microbial signaling. Future regenerative approaches should consider microbiome-aware design (e.g., barrier-restoring agents combined with probiotic or EV-based modulators).

Schematic of mesenchymal stem cell (MSC) therapy. MSCs administered via systemic or intranasal injection home to inflamed nasal tissue. Upon arrival, they exert a dual therapeutic effect by modulating the local immune response (e.g., suppressing Th2 activation and eosinophil infiltration) and promoting tissue repair through the secretion of restorative factors that enhance epithelial barrier integrity (see **Figure 1**).

4. CURRENT THERAPIES AND LIMITATIONS

Management strategies vary by subtype and severity. In AR, allergen avoidance is recommended but rarely feasible. Intranasal corticosteroids remain the most effective monotherapy, reducing both nasal and ocular symptoms. Antihistamines provide rapid relief but are less effective for congestion. Saline irrigation serves as an adjunctive measure. Leukotriene receptor antagonists (e.g., montelukast) offer modest benefit, particularly in patients with asthma. Decongestants are limited by tachyphylaxis and risk of rhinitis medicamentosa. Allergen immunotherapy (SCIT, SLIT) is the only established disease-modifying intervention but requires prolonged treatment and carries risks [2].

Biologics targeting IgE (omalizumab) or type 2 cytokines (dupilumab, mepolizumab) show promise in severe disease, though their cost and uncertain long-term safety limit widespread use [8]. Current treatments remain largely symptomatic and fail to correct epithelial dysfunction or structural damage, underscoring the need for regenerative strategies.

5. *IN VITRO* MODELS FOR STUDYING RHINITIS

Preclinical models are essential for therapeutic discovery. Conventional 2D epithelial cultures lack complexity. Air-liquid interface (ALI) cultures improve physiological relevance by supporting differentiation into ciliated and mucus-secreting phenotypes but remain simplistic. Three-dimensional nasal organoids represent a major advance, recapitulating the architecture and barrier function of native mucosa [9]. These models enable study of epithelial-immune crosstalk, allergen responses, and viral infections (e.g., SARS-CoV-2), making them powerful tools for rhinitis research.

Patient-derived organoids are particularly valuable as they preserve donor-specific genetic and epigenetic signatures, allowing exploration of personalized disease phenotypes [10]. When coupled with CRISPR-Cas9 genome editing, nasal organoids can model the effect of candidate gene variants in barrier integrity and immune responses, providing mechanistic insights into susceptibility and drug response.

6. ORGANOIDS AND STEM CELL BIOLOGY

Organoids are three-dimensional, self-organizing structures that recapitulate essential features of native organs. They arise from the ability of stem cells to self-renew and differentiate in a supportive 3D niche. These constructs reproduce cellular heterogeneity and retain long-term proliferative potential. For nasal applications, organoids mimic ciliated epithelium and neuronal-like structures, providing physiologically relevant systems for modeling rhinitis pathogenesis.

Organoids have broad applications in biomedical research: patient-specific disease modeling, precision drug testing, toxicology, and regenerative medicine. In nasal biology, they allow high-resolution study of allergen responses and immune-epithelial interactions. Stem cells underpin organoid technology, classified as totipotent, pluripotent, oligopotent, or unipotent. Pluripotent stem cells (ESCs, iPSCs) are particularly valuable for generating diverse nasal epithelial lineages. Matrix cues such as Matrigel and morphogen gradients (e.g., EGF, BMP, TGF-β) orchestrate differentiation into basal, goblet, and ciliated cells.

Beyond disease modeling, organoids may also serve as transplantable grafts. Advances in scaling and vascularization techniques are bringing closer the possibility of bioengineered nasal epithelia for clinical use [11]. For example, layering nasal epithelial organoids onto decellularized scaffolds may provide a functional mucosal substitute in cases of rhinitis complicated by mucosal loss.

7. STEM CELL THERAPY IN RHINITIS

Stem cell therapy aims to restore mucosal integrity and immune balance. MSCs are of particular interest, derived from adipose tissue, nasal mucosa, bone marrow, or umbilical cord. They exert immunomodulatory effects, home to inflamed mucosa, and exhibit low immunogenicity. Preclinical murine studies show that MSCs reduce IgE, suppress eosinophilia, and repair epithelial barrier dysfunction [9]. Adipose-derived MSCs also normalize Th1/Th2 balance and improve histology. These mechanisms mirror evidence from inflammatory bowel disease and asthma, and are directly supported in allergic rhinitis models using adipose- and nasal mucosa-derived MSCs with improvements in Th1/Th2 balance and mucosal histology.

The parallels between Crohn's disease and rhinitis highlight feasibility: both are chronic inflammatory conditions where MSCs suppress hyperactive immunity and promote tissue repair. Early preclinical results in rhinitis support clinical translation, though variability in culture protocols, optimal administration route, and safety remain barriers.

Emerging studies suggest MSCs exert effects largely via paracrine signaling—secreting exosomes, cytokines, and growth factors that reprogram local immune responses and stimulate epithelial repair [12]. Harnessing extracellular vesicles (EVs) derived from MSCs may provide a safer, cell-free therapeutic alternative, reducing risks of ectopic differentiation or tumorigenesis. Nasal delivery of MSC-derived EVs is under early investigation and may offer a novel regenerative approach. Relative to whole-cell MSC therapies, MSC-derived extracellular vesicles (EVs) show lower immunogenicity and eliminate engraftment/tumorigenicity risks; practical advantages include sterilizable, lyophilizable formulations and consistent potency assays. Intranasal or hydrogel-assisted delivery of MSC-EVs has alleviated AR pathology in mice, restoring epithelial barrier and rebalancing Th1/Th2 responses.

8. TISSUE ENGINEERING APPROACHES

Building on stem cell therapy, tissue engineering (TE) provides structural repair for nasal tissues damaged by inflammation, trauma, or surgery. TE combines living cells, biomaterials, and bioactive signals to restore mucosa, cartilage, and skin.

Mucosal regeneration: Biological scaffolds such as collagen sponges or decellularized matrices seeded with fibroblasts, epithelial progenitors, or MSCs recreate mucosal lining. These grafts restore humidification, barrier function, and reduce symptoms like dryness or crusting. Tissue-engineered mucosa may treat septal perforations and empty nose syndrome (ENS) [13].

Cartilage engineering: Damaged nasal cartilage worsens airflow obstruction. Hydrogels, 3D-printed matrices, and electrospun fibers seeded with chondrocytes or MSCs, supplemented by TGF-β, enable cartilage regeneration. Pilot clinical studies show engineered cartilage implants can correct nasal deformities without requiring donor grafts [14].

Skin regeneration: Though less directly tied to rhinitis, external nasal defects from surgery or chronic inflammation can be repaired with acellular dermal matrices or collagen-based scaffolds. Early progress in vascularized skin equivalents may ultimately enable integration with mucosal and cartilage constructs.

Challenges for TE include scaffold durability, immune rejection, vascularization, and GMP-compliant scaling. Recent advances in 3D bioprinting, patient-specific computer-aided design, and biomaterials with controlled release of growth factors are improving outcomes [15]. Combining stem cells with smart scaffolds holds potential to restore both form and function of nasal tissues.

Strategy for Engineering Functional Nasal Tissue Constructs. The combination of seed cells, a biodegradable scaffold, and bioactive growth factors enables the *in vitro* generation of a functional graft. This construct can be implanted to repair structural defects, such as a septal perforation, facilitating integration and restoration of nasal mucosa and cartilage (see **Figure 2**).

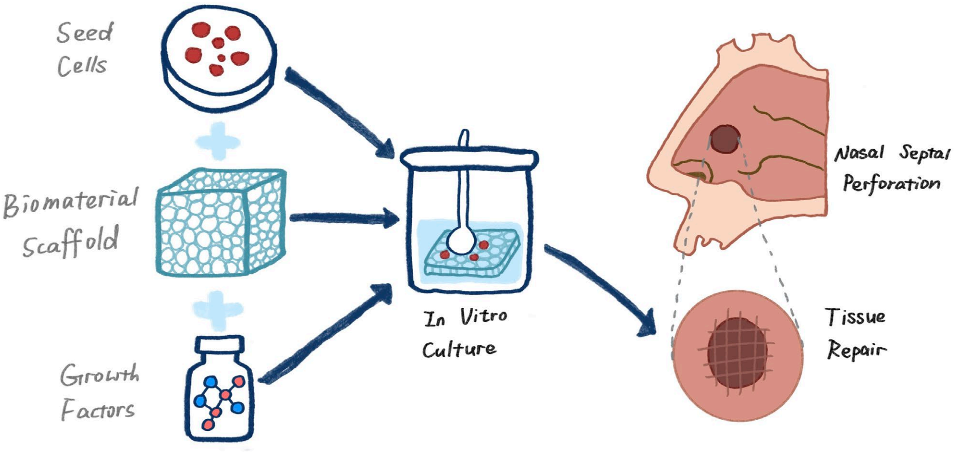

Figure 2. **Tissue engineering approach for nasal defects.**

9. FUTURE DIRECTIONS

Future rhinitis therapies will integrate organoids, stem cells, and TE. MSCs seeded on 3D scaffolds may provide immunomodulation plus structural restoration. Organoid-derived epithelia layered on engineered matrices could recreate nasal mucosa. Gene-edited iPSCs may yield rejection-resistant grafts. Coupled with omics and spatial transcriptomics, these tools will enable precise targeting of disease pathways [16]. Translation and regulation: Any cell/EV product for rhinitis will be an ATMP in the EU/UK and must meet GMP-grade sourcing, release testing (identity, purity, potency), and stability requirements; early engagement with EMA/MHRA advice can de-risk development. Beyond safety/efficacy, demonstration of value to payers (HTA) and scalable manufacturing will be decisive.

Personalized regenerative medicine is likely to emerge, leveraging patient-derived iPSCs and organoids to tailor grafts. Cell-free therapies using MSC exosomes may complement tissue-engineered implants. Interdisciplinary collaboration will accelerate progress, while regulatory frameworks must balance innovation with safety.

10. CONCLUSION

Rhinitis imposes a major global health burden, yet current therapies remain largely symptomatic. Organoid models, stem cell therapy, and tissue engineering are opening regenerative pathways to address epithelial and immune dysfunction. Overcoming translational challenges will be key, but regenerative medicine has the potential to shift rhinitis management from palliation to restoration.

CONFLICTS OF INTEREST

The author declares no conflicts of interest regarding the publication of this paper.

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