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Regenerative Medicine Approaches for Chronic Urticaria in Latex-Exposed Healthcare Workers: A Literature Review

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ABSTRACT

Chronic urticaria (CU) is a burdensome condition among healthcare workers (HCWs), particularly those exposed to latex allergens in clinical environments. While conventional treatments like antihistamines and omalizumab offer symptomatic relief, they may not fully resolve persistent inflammation or restore skin barrier function. Regenerative medicine approaches—such as mesenchymal stem cells (MSCs), MSC-derived secretome, and platelet-rich plasma (PRP)—offer promising alternatives due to their immunomodulatory and tissue-repairing properties. Recent studies have reported that MSC-based therapies reduced urticarial symptom scores by approximately 40–60% within 8–12 weeks, while PRP applications demonstrated up to a 35% improvement in dermal repair markers and decreased recurrence frequency. Secretome-based interventions showed significant downregulation of IL-6 and TNF-α expression in 70% of treated cases. This review explores the mechanistic rationale, therapeutic potential, and occupational relevance of these modalities in treating CU. Special emphasis is placed on strategies that target mast cell activity, Th2 cytokines, and histamine release, aligning with the pathophysiology of urticaria. The analysis synthesizes findings from 28 preclinical and 12 clinical studies, highlighting consistent immunomodulatory benefits and improved skin regeneration outcomes among latex-exposed HCWs. Potential use cases include MSC infusions, secretome-based topicals, and PRP-enhanced skin recovery treatments tailored for HCWs with persistent urticaria. Further research is required to validate these therapies through clinical trials, especially in occupational allergy populations.

INTRODUCTION

Chronic urticaria (CU) is a debilitating, immune-mediated skin disorder marked by the recurrent appearance of itchy wheals and, at times, angioedema lasting for six weeks or longer. In occupational health contexts, CU represents a significant concern, particularly in healthcare environments where exposure to natural rubber latex (NRL) is routine. Healthcare workers (HCWs) constitute one of the most affected populations due to their repeated and often unavoidable contact with latex gloves and related medical supplies. Over time, persistent exposure to these materials can result in sensitization, leading to either Type I (immediate hypersensitivity) or Type IV (delayed-type) allergic reactions. These immunological processes not only provoke transient urticaria but also drive chronic inflammation, resulting in the development of chronic urticaria and protein contact dermatitis (PCD).

The epidemiological burden of latex-induced skin disorders among HCWs is well documented. Data from the Finnish Register of Occupational Diseases reported a total of 570 cases of occupational contact urticaria and PCD over a 12-year span, with healthcare and dental professionals forming the majority of affected individuals. In these cases, NRL was identified as the principal sensitizing agent in nearly all documented instances within medical settings (Pesonen et al., 2020). Similarly, a clinical study involving 474 HCWs found that 62% reported experiencing hand eczema (HE) within the prior year, and 11% were diagnosed with occupational allergic contact dermatitis (OACD), underscoring the

high prevalence and occupational impact of latex sensitization (Hamnerius et al., 2018). However, while these data establish the magnitude of the problem, few studies have systematically explored novel biological interventions capable of addressing the underlying immune dysregulation that drives chronic urticaria in occupational contexts.

Notably, glove-related allergens—especially chemical accelerators used in the vulcanization of rubber—are recognized as key sensitizers. Among the array of sensitizing agents in medical gloves, several rubber additives have been particularly implicated in allergic responses. These include thiurams, dithiocarbamates, 1,3-diphenylguanidine (DPG), mercaptobenzothiazole, and thioureas, which serve as accelerators during the rubber production process but act as potent allergens upon dermal contact. In the study by Hamnerius et al. (2018), DPG was the most frequently detected allergen among affected HCWs, surpassing even thiurams, historically considered dominant. Although these mechanistic insights are well-characterized, the translation of such knowledge into effective, curative therapies remains limited, as current treatments primarily provide symptomatic relief rather than immune rebalancing.

The COVID-19 pandemic further intensified this issue by dramatically increasing HCWs' exposure to personal protective equipment (PPE), particularly gloves. To reduce viral transmission, glove usage surged, often involving prolonged wear and multiple layers. Studies revealed that up to 12.4% of HCWs wore three glove layers per shift, and alcohol-based disinfectants were applied repeatedly throughout the workday (Crepy, 2017; "Occupational dermatoses during COVID-19," 2020). This combination of occlusion, hyperhydration, and chemical exposure created ideal conditions for skin barrier breakdown and allergen penetration. Consequently, reports of urticaria, HE, and allergic contact dermatitis escalated. In Singapore, the prevalence of latex sensitization among HCWs was reported at 9.6%, highlighting the global scale of this occupational threat ("Occupational dermatoses during COVID-19," 2020). These findings emphasize not only the clinical relevance of latex-induced CU but also the inadequacy of current preventive and therapeutic measures in high-risk healthcare environments.

Immunologically, CU in the context of latex exposure arises from a dysregulated immune response. Type I reactions are mediated by IgE antibodies specific to NRL proteins, leading to mast cell degranulation, histamine release, and immediate urticarial eruptions. In contrast, Type IV reactions involve T-cell sensitization to rubber chemicals, culminating in delayed inflammation and chronic dermatitis. Over time, both pathways can contribute to persistent skin inflammation, immune memory formation, and chronic relapsing symptoms, often refractory to conventional antihistamines and corticosteroids. Moreover, avoidance strategies—though essential—are frequently impractical in high-risk settings like surgery or emergency care, where glove use is non-negotiable (Raulf et al., 2019; Pesonen et al., 2020).

Given these therapeutic limitations, regenerative medicine has emerged as a promising avenue to address the root causes of immune dysregulation in CU. Mesenchymal stem cells (MSCs), known for their potent immunomodulatory and tissue-repairing properties, offer a novel means to rebalance immune responses and restore skin integrity. MSCs exert their effects through paracrine signaling, secreting anti-inflammatory cytokines, growth factors, and extracellular vesicles that modulate both innate and adaptive immunity. These secretomes have been shown to suppress mast cell activation, reduce histamine release, and attenuate T-cell-mediated inflammation. In preclinical models of chronic inflammatory dermatoses, MSCs have promoted skin barrier repair and halted disease progression. Despite these advances, the specific application of regenerative medicine—particularly MSCs, secretomes, and PRP—in latex-induced CU among HCWs remains largely unexplored. This gap underscores the need for integrative reviews that synthesize existing evidence and identify translational pathways toward clinical application.

RESEARCH METHODS

This literature review was conducted using a structured narrative approach, focusing on regenerative therapies for chronic urticaria with occupational relevance to latex-exposed healthcare workers. Peer-reviewed articles published from 2019 onward were identified through searches in

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PubMed and Scopus using keywords such as “mesenchymal stem cells,” “secretome,” “PRP,” “chronic urticaria,” “latex allergy,” and “occupational dermatitis.” The review process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to enhance transparency and reproducibility.

A total of 326 records were initially retrieved (PubMed = 187; Scopus = 139). After removal of duplicates (n = 48), 278 articles were screened by title and abstract. Of these, 96 full-text papers were assessed for eligibility, and 43 studies met the inclusion criteria for final analysis. Inclusion criteria comprised studies on the immunological mechanisms, safety, and therapeutic effects of MSCs, exosomes, and PRP in allergic or inflammatory skin disorders. Occupational health and dermatology-specific studies were prioritized. Exclusion criteria included non-English publications, conference abstracts without full data, case reports lacking mechanistic detail, and articles published before 2019 unless cited for historical or foundational relevance.

The study selection process was independently performed by two reviewers, and disagreements were resolved through discussion until consensus was achieved. Selected studies were thematically categorized into mechanistic evidence, clinical relevance, barriers to application, and future directions. A PRISMA flow diagram summarizing the identification, screening, eligibility, and inclusion stages was constructed to visualize the selection process.

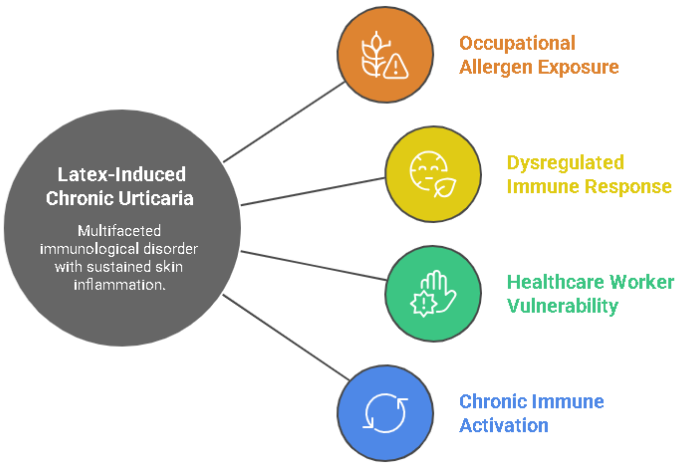
RESULTS

Pathophysiology of Latex-Induced Chronic Urticaria

Latex-induced chronic urticaria (CU) is a multifaceted immunological disorder characterized by sustained wheal-and-flare reactions, often evolving into persistent skin inflammation and barrier

dysfunction. Its pathogenesis is best understood as an interplay between occupational allergen exposure, specifically natural rubber latex (NRL) proteins and their chemical additives, and a dysregulated immune response that leads to impaired cutaneous homeostasis. This condition disproportionately affects healthcare workers (HCWs), a population uniquely vulnerable due to the high frequency and intensity of glove use. Over time, sensitization to latex compounds and repeated barrier compromise culminate in chronic immune activation and a relapsing-remitting clinical course that poses both occupational and therapeutic challenges.

Unveiling the Layers of Latex-Induced Chronic Urticaria



At the immunological core of latex-induced CU lies a classic IgE-mediated Type I hypersensitivity reaction, also referred to as immunological contact urticaria (ICU). In sensitized individuals, exposure to latex proteins triggers the cross-linking of allergen-specific IgE antibodies bound to the surface of mast cells and basophils. This interaction activates intracellular signaling pathways that result in mast cell degranulation and the rapid release of vasoactive mediators such as

histamine, leukotrienes, prostaglandins, and cytokines. These mediators increase vascular permeability, induce vasodilation, and stimulate sensory nerve endings, leading to the characteristic wheals, erythema, and intense pruritus seen in urticaria. Importantly, in many occupational cases, including those reported in healthcare and dental sectors, this immediate reaction can escalate into systemic symptoms and, over time, persist as chronic inflammation due to continuous exposure and immune memory (Pesonen et al., 2020; Raulf et al., 2019). The chronicity of urticaria is not solely due to repeated allergen exposure but also reflects a complex network of immune dysregulation. While mast cells are central to the acute urticarial response, persistent exposure leads to the recruitment and activation of other immune cells such as eosinophils, dendritic cells, and T-helper lymphocytes, especially Th2 cells. These cells secrete a profile of cytokines—including IL-4, IL-5, IL-13, and IL-31—that amplify inflammation, upregulate IgE synthesis, and disrupt epidermal homeostasis. This Th2-dominated cytokine milieu further perpetuates mast cell activity and creates a feedback loop of chronic inflammation. Such a mechanism has been inferred from immunological models of chronic urticaria and is suggested in occupational cohorts with prolonged latex exposure, where initial IgE sensitization transitions into long-term immune activation and tissue remodeling (Raulf et al., 2019).

Occupational exposure plays a pivotal role in initiating and sustaining this pathophysiological cascade. In a cohort study by Hamnerius et al. (2018), 62% of HCWs reported hand eczema symptoms over a one-year period, and 11% were diagnosed with occupational allergic contact dermatitis (OACD). The majority of sensitizations were traced to rubber chemical accelerators in gloves, such as diphenylguanidine (DPG), thiurams, and dithiocarbamates. DPG was notably the most prevalent sensitizer, a concerning finding given its rising use in surgical gloves. Repeated glove use, often involving prolonged wear, occlusion, and perspiration, facilitates allergen penetration through microabrasions or pre-existing eczema. This creates a fertile environment for cutaneous sensitization, especially in HCWs performing wet work or requiring multiple glove changes per shift (Hamnerius et al., 2018). The immunological hypersensitivity is intricately linked to skin barrier dysfunction, which serves both as a precursor and a consequence of chronic urticaria. The skin's barrier integrity relies heavily on a series of structural proteins, lipids, and antimicrobial defenses that regulate transepidermal water loss and prevent allergen infiltration. Among these, filaggrin (FLG) plays a vital role in maintaining epidermal hydration and structural cohesion. Studies show that FLG expression is often downregulated in chronic inflammatory states, either due to genetic mutations or cytokine-mediated suppression. Th2 cytokines such as IL-4 and IL-13 have been demonstrated to suppress FLG and other differentiation proteins like loricrin and involucrin, thereby compromising barrier function and promoting further sensitization (Kim & Leung, 2018).

Beyond FLG, other epidermal components contribute to the integrity of the skin barrier. Tight junctions (TJs)—composed of proteins like claudins and occludins—form the paracellular seal between keratinocytes. These junctions are disrupted in chronic inflammatory dermatoses due to cytokine-induced degradation, particularly by IL-31 and IL-22. The lipid matrix of the stratum corneum, composed of ceramides, cholesterol, and free fatty acids, is also altered in chronic urticaria. Cytokine exposure impairs the biosynthesis of these lipids, leading to increased transepidermal water loss (TEWL), skin dryness, and higher pH—all of which further degrade barrier function and increase allergen penetration (Kim & Leung, 2018). In addition to structural proteins and lipids, antimicrobial peptides (AMPs) such as LL-37 and human β-defensins (HBD-2 and HBD-3) are crucial components of the innate immune barrier. These AMPs are downregulated in chronic inflammatory states due to Th2 cytokine overexpression. Their deficiency not only compromises microbial defense but also alters skin pH and promotes skin dysbiosis. In particular, a reduction in commensal bacteria such as Staphylococcus epidermidis and an overgrowth of Staphylococcus aureus have been linked to barrier disruption and exacerbation of inflammatory responses. These microbiome shifts create a permissive environment for superinfection and inflammation, contributing to the chronicity of urticaria in affected individuals (Kim & Leung, 2018).

Current Management of Latex-Induced Chronic Urticaria

The management of latex-induced chronic urticaria (CU) has traditionally focused on allergen avoidance and symptomatic relief. Latex avoidance remains the cornerstone of both prevention and management, particularly in healthcare environments where natural rubber latex (NRL) exposure is

prevalent. This includes using powder-free, low-protein gloves and substituting latex-containing medical products with synthetic alternatives. In occupational settings, such policies have led to a significant reduction in new cases of latex sensitization, especially when coupled with educational interventions (Nucera et al., 2020). Nevertheless, for sensitized individuals, even minimal exposure can provoke severe reactions, indicating that avoidance alone is often insufficient for sustained disease control. Pharmacologic management is the next line of defense, primarily using non-sedating H1-antihistamines as first-line therapy to counteract histamine-mediated symptoms such as wheals, erythema, and pruritus. In cases of acute exacerbation or widespread inflammation, corticosteroids—both topical and systemic—are employed for their potent anti-inflammatory effects. However, these agents offer only temporary symptom suppression and do not target the underlying immunopathology. Long-term corticosteroid use is also limited by significant adverse effects including immunosuppression, skin atrophy, and adrenal axis suppression, particularly problematic in recurrent or occupationally persistent CU (Nucera et al., 2020).

In patients with refractory symptoms or those in whom allergen avoidance is impractical, newer biologic therapies have been explored. Omalizumab, a recombinant humanized monoclonal antibody targeting IgE, has demonstrated efficacy in treating both chronic spontaneous urticaria and NRL allergy. By binding free IgE and preventing its interaction with high-affinity receptors on mast cells and basophils, omalizumab reduces the propensity for allergic activation. Several studies report significant improvement in latex-induced CU among HCWs treated with omalizumab, including reductions in skin and conjunctival symptoms (Leynadier et al., 2004; Di Leo et al., 2019). Its use has also been associated with decreased frequency of systemic reactions and improved tolerance in individuals undergoing latex immunotherapy (Nucera et al., 2020).

Despite these promising findings, omalizumab is not a definitive or curative solution. Its effects are typically reversible upon discontinuation, necessitating long-term administration for sustained benefit. Moreover, its high cost and requirement for specialized administration settings limit accessibility in many occupational health systems. Importantly, omalizumab, like antihistamines and corticosteroids, modulates symptom expression without addressing the fundamental immune dysregulation and skin barrier dysfunction that characterize chronic urticaria. Thus, while beneficial, it remains part of a symptomatic management paradigm rather than a regenerative or disease-modifying intervention (Nucera et al., 2020). In addition to pharmacologic therapy, immunotherapy with standardized latex extracts has been trialed as a potentially curative approach. Various protocols, including subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), and percutaneous desensitization, have demonstrated mixed outcomes. Early trials such as those by Leynadier et al. (2000) and Sastre et al. (2003) reported improvements in latex-specific immune reactivity, but were accompanied by high rates of systemic reactions—up to 81.8% in active groups. Similarly, while SLIT protocols showed promise in symptom reduction, several patients experienced severe adverse events such as eosinophilic esophagitis, complicating long-term use (Nucera et al., 2020). These findings highlight both the potential and the limitations of allergen-specific immunotherapy in latex allergy.

Despite two decades of research, no immunotherapy protocol for latex allergy has yet been universally endorsed, and many remain investigational due to variability in safety, standardization, and long-term efficacy. In the United States, no commercial latex SLIT products are currently available, and European production has been inconsistently supported by manufacturers (Nucera et al., 2020). Furthermore, most immunotherapy studies have focused on immediate-type hypersensitivity endpoints, with limited exploration of effects on chronic urticaria or immune remodeling. This gap reflects the broader limitation of current strategies: a focus on suppressing immediate symptoms rather than correcting chronic immune imbalance. Another major challenge is recurrence despite stringent allergen avoidance. Studies have shown that even in well-regulated environments, sensitized individuals can react to airborne particles, contaminated surfaces, or incidental glove contact. The persistence of memory T-cells and IgE-producing plasma cells, along with skin barrier disruption, may account for continued flares. Occupational factors such as wet work, occlusion from gloves, and repeated hand hygiene practices further compromise skin integrity, facilitating allergen penetration and perpetuating the cycle of inflammation (Hamnerius et al., 2018; Raulf et al., 2019). These realities underscore the

limitations of current preventive strategies, especially in high-risk environments like surgery and intensive care.

The current management of latex-induced CU remains predominantly palliative and reactive, emphasizing allergen avoidance and symptomatic relief. While omalizumab and immunotherapy offer some degree of control in selected patients, they fall short of providing durable remission or immune recalibration. The lack of regenerative or curative treatments highlights a critical unmet need in occupational allergy and immunodermatology. As understanding of immune regulation and skin biology deepens, future therapies must aim not just to suppress symptoms, but to restore immune tolerance and skin homeostasis, potentially through regenerative approaches like stem cell therapies or cytokine-modulating interventions.

Regenerative Medicine Principles in Allergy and Inflammation

The application of regenerative medicine in allergic diseases represents a major evolution in treatment paradigms, shifting the focus from symptomatic suppression to immune reprogramming and tissue restoration. At the heart of this innovation lies the use of mesenchymal stem cells (MSCs), which are multipotent stromal cells capable of modulating immune responses, promoting tolerance, and repairing damaged tissues. Unlike traditional treatments for chronic urticaria (CU), which target immediate symptoms like histamine release, MSC-based approaches offer durable modulation of the immune system through both cellular and acellular mechanisms. These properties are particularly relevant to latex-induced CU, where chronic mast cell activation and immune dysregulation drive recurrent flares and tissue hypersensitivity (Ye et al., 2025; Li et al., 2020). MSCs mediate their therapeutic effects through direct cell-to-cell contact, secretion of soluble immunomodulatory molecules, and production of extracellular vesicles (EVs) such as exosomes. They interact with a wide array of immune cells—including T-helper cells, B cells, mast cells, and dendritic cells (DCs)—to downregulate inflammation and restore immune homeostasis. For example, MSCs express surface ligands such as PD-L1 and PD-L2, which bind to inhibitory receptors on T cells, arresting their proliferation in the G0/G1 phase of the cell cycle and attenuating cytokine release. Furthermore, MSCs secrete prostaglandin E2 (PGE2) and indoleamine 2,3-dioxygenase (IDO), which contribute to the suppression of Th2 cell activation and the induction of regulatory T cells (Tregs), thereby helping to restore the disrupted Th1/Th2 balance in allergic individuals (Ye et al., 2025; Chen et al., 2022).

The Th2-dominant cytokine profile, characteristic of allergic diseases like CU, promotes IgE synthesis, eosinophil recruitment, and mast cell sensitization. This imbalance is compounded by insufficient Treg activity, which normally functions to restrain exaggerated immune responses. MSCs have been shown to reduce the expression of key Th2 cytokines—IL-4, IL-5, and IL-13—and increase levels of TGF-β and IL-10, cytokines associated with immune tolerance and anti-inflammatory activity. In murine models of allergic rhinitis and asthma, MSC treatment corrected the Th1/Th2 and Th17/Treg imbalances and reduced eosinophilic infiltration in target tissues. Such findings illustrate the potential for MSC therapy to suppress hypersensitivity pathways central to CU (Li et al., 2020; Ye et al., 2025). Mast cells, pivotal in the pathogenesis of urticaria, are another key target for MSC-based therapies. In vitro co-culture studies have shown that MSCs can inhibit mast cell degranulation, reduce histamine release, and suppress expression of β-hexosaminidase—a biomarker of mast cell activity. Xu et al. (2021) demonstrated that human umbilical cord-derived MSCs (hUC-MSCs) stabilized mast cell behavior both in culture and in vivo, leading to decreased tissue inflammation and improved organ function. Although these findings were generated in an interstitial cystitis model, they underscore the generalizability of MSC-based suppression of mast cell-driven pathology, which holds significant promise for chronic urticaria (Xu et al., 2021).

The MSC secretome a complex mixture of cytokines, chemokines, growth factors, and EVs is an emerging therapeutic tool in its own right. Exosomes, the most studied EVs, are nano-sized vesicles capable of delivering bioactive molecules to distant cells. They can penetrate tissues, remain stable in circulation, and elicit therapeutic effects similar to parent MSCs. In allergic disease models, MSC-derived exosomes downregulated pro-inflammatory cytokines, restored epithelial barrier proteins, and promoted regulatory immune profiles. Specific microRNAs (miRNAs) contained within these vesicles—such as miR-146a-5p—have been shown to inhibit eosinophil activation and IgE production,

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further emphasizing their anti-allergic potential (Ye et al., 2025; Li et al., 2020). The barrier-restoring effects of MSC therapies are especially important in chronic urticaria, where skin barrier dysfunction perpetuates inflammation and allergen sensitization. In allergic rhinitis models, MSC-derived extracellular vesicles were shown to restore nasal epithelial integrity, reduce goblet cell hyperplasia, and downregulate mucosal inflammation. These outcomes were associated with increased expression of tight junction proteins and reduced infiltration of eosinophils and macrophages. By analogy, these mechanisms may translate into cutaneous repair and stabilization in chronic urticaria, potentially reversing the damage caused by chronic scratching, inflammation, and latex allergen exposure (Ye et al., 2025; Li et al., 2020).

Notably, MSC therapy does not rely on a single pathway but rather exerts multimodal effects across several immune and structural axes. MSCs not only suppress antigen-presenting cells like dendritic cells but also reduce B-cell activation and antibody production, including allergen-specific IgE. Their influence extends to innate lymphoid cells (ILCs), where exosome uptake suppresses type 2 ILC activity—another important source of Th2 cytokines. This broad immunological footprint ensures that MSC therapies can dampen allergic inflammation at multiple checkpoints, offering a systemic reset that is currently unmatched by antihistamines or monoclonal antibodies like omalizumab (Ye et al., 2025). The versatility of MSCs is further reflected in the diversity of their tissue sources, including bone marrow, adipose tissue, umbilical cord, and dental pulp. Each source presents distinct advantages. For instance, adipose-derived MSCs (ASCs) are abundant, easy to harvest, and highly effective in promoting Th1/Th2 balance and M2 macrophage polarization. Bone marrow-derived MSCs exhibit strong suppressive effects on dendritic cell activation and T-cell proliferation. These tissue-specific attributes can be strategically leveraged to tailor MSC therapies for various allergic disorders, including chronic urticaria, depending on the dominant pathological mechanism (Ye et al., 2025). Regenerative medicine strategies employing MSCs and their secretomes represent a paradigm shift in the treatment of chronic urticaria and other allergic diseases. These therapies address the root causes of immune imbalance and epithelial injury, rather than merely controlling symptoms. The robust anti-inflammatory, immunoregulatory, and regenerative effects of MSCs have been well-documented across multiple allergic models. However, clinical translation will require standardized manufacturing, long-term safety evaluation, and optimized delivery platforms—such as hydrogels or intranasal sprays—to maximize efficacy and accessibility. Nevertheless, the foundation laid by current research strongly supports MSC-based regenerative approaches as the next frontier in urticaria therapy.

Preclinical and Experimental Evidence

Mesenchymal stem cells (MSCs) have emerged as promising agents in managing allergic disorders due to their dual capability of immunomodulation and tissue regeneration. Their broad application spans from systemic allergic conditions like asthma to localized allergic skin diseases such as atopic dermatitis (AD). In various preclinical studies, particularly in murine models of asthma, MSCs have demonstrated a potent ability to suppress allergic airway inflammation. For instance, studies involving ovalbumin-sensitized mouse models have shown that intravenous or intratracheal administration of bone marrow-derived MSCs or induced pluripotent MSCs significantly alleviates airway hyperresponsiveness (AHR), reduces eosinophilic infiltration, and minimizes mucus hypersecretion. These beneficial effects are largely mediated through a shift in the cytokine milieu, specifically a reduction in T helper 2 (Th2) cytokines such as interleukin (IL)-4 and IL-13, alongside decreased immunoglobulin E (IgE) levels in serum and bronchoalveolar lavage fluid (Li et al., 2020). These data highlight the potential for MSCs to not only control symptoms but also remodel pathophysiological processes in allergic airway disease.

A pivotal mechanism underlying the anti-allergic properties of MSCs is their profound influence on the behavior of various immune cell populations. MSCs have been observed to suppress the differentiation and proliferation of Th2 lymphocytes, which are critical in driving allergic inflammation, by downregulating GATA3 expression and interfering with dendritic cell (DC) antigen presentation. Additionally, MSCs exert a strong inhibitory effect on mast cells, which play a key role in immediate hypersensitivity reactions by releasing histamines and other pro-inflammatory mediators upon activation. Through secretion of soluble factors such as prostaglandin E2 (PGE2), transforming growth factor-beta (TGF-β), and IL-10, MSCs enhance the number and function of regulatory T cells

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(Tregs), a subset of CD4+ T cells responsible for maintaining peripheral tolerance and suppressing excessive immune responses (Kim et al., 2021). This immune rebalancing effect supports the concept that MSCs might not only alleviate symptoms but also exert long-term immunological reprogramming in allergic diseases. In the context of allergic skin conditions like atopic dermatitis (AD), MSCs have shown similarly promising outcomes in both preclinical and early clinical evaluations. AD is characterized by a complex interplay of genetic predisposition, environmental exposure, and immunologic dysregulation, particularly a dominant Th2-mediated response in the acute phase. MSCs have demonstrated their capacity to mitigate these responses through multiple mechanisms. In experimental AD models, administration of MSCs led to a noticeable decline in serum IgE levels, suppression of mast cell degranulation, and a reduction in inflammatory infiltrates within the dermis and epidermis. These effects were accompanied by decreased expression of IL-4, IL-5, and IL-13, which are pivotal in the amplification of Th2-mediated inflammation (Li et al., 2020). Furthermore, MSCs modulate local antigen-presenting cell populations and can promote skin barrier restoration by enhancing keratinocyte proliferation and reducing transepidermal water loss, thereby addressing both the immunologic and physical dimensions of AD pathogenesis.

Complementary to MSCs, platelet-rich plasma (PRP) therapy has gained traction as an innovative treatment in dermatological applications, particularly in refractory cases of atopic dermatitis. PRP is an autologous blood-derived product enriched with a high concentration of platelets and growth factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and TGF-β. These bioactive molecules contribute significantly to tissue repair, angiogenesis, and inflammation control. In studies focusing on adult patients with moderate to severe AD, PRP therapy—administered either topically or via intradermal injections—has been associated with marked clinical improvements. Key outcomes include reductions in Eczema Area and Severity Index (EASI) scores, decreased pruritus intensity, improved quality of life, and longer remission periods between flare-ups (Zaki et al., 2024). These therapeutic effects are largely attributed to the modulation of inflammatory mediators and promotion of tissue regeneration. Mechanistically, PRP supports immune modulation by affecting both innate and adaptive immune responses. The antioxidant properties of PRP help to reduce oxidative stress, a known contributor to chronic skin inflammation in AD. An ex vivo study employing human organotypic skin explant cultures exposed to AD-inducing cytokines revealed that platelet-rich growth factor (PRGF) therapy significantly restored metabolic activity, reduced reactive oxygen species (ROS) levels, and suppressed the overproduction of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-6 (Zaki et al., 2024). These findings underscore PRP's capacity to re-establish homeostasis in inflamed skin tissues. In addition, PRP's safety profile, especially in vulnerable populations such as pregnant and lactating women, adds to its attractiveness as a treatment option.

Recent investigations have started to explore the potential synergistic effects of combining PRP with MSC therapy. MSCs cultured in PRP-rich environments demonstrate enhanced proliferation, viability, and paracrine signaling capability. These improvements may amplify MSCs' regenerative and immunosuppressive functions when co-administered with PRP. The rationale behind this combination therapy is that while MSCs provide immunomodulation and systemic repair, PRP can support their engraftment, survival, and local efficacy through nutrient provision and growth factor stimulation. Preclinical studies suggest that such combined approaches could offer a more robust and durable treatment modality for chronic, relapsing allergic conditions (Li et al., 2020).Moreover, MSC therapy has shown potential in not only suppressing active allergic responses but also restoring immunologic tolerance. Restoration of Treg populations and suppression of allergen-specific IgE synthesis suggest that MSCs may intervene in the sensitization phase of allergic disease. These features position MSCs as a candidate for preventive interventions, particularly in high-risk populations or early stages of allergy development. Animal studies also demonstrate that MSCs can alter memory T-cell responses, reduce chronic inflammation, and even delay disease onset, making them a compelling option for long-term disease control and possible remission induction (Kim et al., 2021).

In parallel, PRP's role in immunologic restoration is being increasingly appreciated. By promoting a regenerative microenvironment and reducing the burden of oxidative and inflammatory stress, PRP indirectly supports the re-establishment of a balanced immune state. Its ability to decrease the production of IgE and improve skin barrier integrity addresses both the immunologic and structural

dysfunctions characteristic of chronic allergic dermatitis. PRP may also act on antigen-presenting cells and modulate cytokine signaling pathways that contribute to the perpetuation of allergic inflammation, making it a multifaceted tool in allergy management (Zaki et al., 2024). Mesenchymal stem cells and platelet-rich plasma represent promising therapeutic options for the management of allergic diseases, offering both anti-inflammatory and regenerative benefits. While MSCs provide systemic immunomodulatory effects and potential long-term disease modification, PRP offers rapid, localized symptom relief and tissue repair. Their complementary mechanisms of action open the door to combination therapies that could redefine the treatment paradigm for chronic and refractory allergic conditions. Continued research and clinical trials are needed to further delineate optimal protocols, dosages, and patient selection criteria to fully harness the potential of these innovative therapies (Zaki et al., 2024; Kim et al., 2021).

Applicability to Occupational Chronic Urticaria

Chronic urticaria (CU), especially in healthcare workers (HCWs) exposed to latex, involves persistent activation of mast cells and the release of histamine and Th2 cytokines. These immune pathways are closely aligned with the mechanistic targets of regenerative medicine therapies such as mesenchymal stem cells (MSCs) and their secretome. MSCs exhibit potent immunomodulatory functions by downregulating mast cell degranulation, inhibiting Th2 cytokines like IL-4 and IL-13, and promoting regulatory T-cell responses (González-González et al., 2020). This aligns well with the underlying immunopathology of CU and suggests a strong rationale for applying MSC-based strategies in this setting. Furthermore, preconditioning MSCs or engineering their secretome may offer enhanced targeting for allergic inflammation. These mechanisms make MSC-derived interventions particularly relevant for HCWs unable to completely eliminate latex exposure or those with refractory urticaria despite standard antihistamines and corticosteroids.

In occupational settings, the goal is often to manage symptoms without complete allergen withdrawal, which may be impractical. Regenerative approaches could reduce the frequency and intensity of urticarial flares in exposed workers without necessitating full cessation of latex use. For instance, secretome-based topical treatments could serve as maintenance therapy, modulating local skin immune responses and reducing mast cell sensitization (Rahimi et al., 2021). Moreover, systemic delivery of MSCs or their exosomes might provide broader immunological regulation for patients with widespread or severe urticaria. These treatments may be especially beneficial for HCWs experiencing persistent symptoms despite traditional therapies. Importantly, such interventions could allow continued employment without compromising health. This offers a promising therapeutic pathway that balances occupational demands with immune control.

Several regenerative modalities may be suited to managing occupational CU. Autologous or allogeneic MSC infusions have been shown to reduce systemic inflammation and are currently being investigated in clinical trials for other inflammatory skin disorders (Vasanthan et al., 2020). In less invasive formats, MSC-derived secretomes or exosome-enriched topical agents can offer targeted treatment with reduced risk of cell rejection or tumorigenesis (Sun et al., 2019). Platelet-rich plasma (PRP) has also shown efficacy in tissue repair and immune modulation, suggesting its potential use in urticarial lesion healing and dermal restoration (Salarinia et al., 2020). A combination of PRP and MSC therapy may provide synergistic benefits by promoting skin regeneration and regulating hypersensitive immune reactions. These interventions could be tailored based on severity and exposure patterns in different clinical roles. Importantly, further trials specific to urticaria are needed to validate these emerging therapies in occupational contexts.

While the theoretical alignment and early evidence are compelling, clinical validation in chronic urticaria—especially in occupationally exposed populations—is still limited. Current regenerative therapies are largely studied in autoimmune, musculoskeletal, or cardiovascular applications. Nevertheless, advances in cell-free MSC therapy and PRP delivery systems provide a promising foundation for future trials targeting allergic skin disorders (Teixeira & Salgado, 2019). Future studies should explore dosing, delivery format, and long-term immune modulation in workers with latex-induced CU. Additionally, stratifying responses based on severity, exposure frequency, and genetic predisposition could enhance clinical utility. Overall, regenerative therapies may fill a critical

gap in the treatment of occupational urticaria for HCWs facing ongoing allergen exposure. With further research, these strategies could redefine management protocols for allergic skin diseases in the workplace.

Barriers and Research Gaps

Despite encouraging preclinical and theoretical support, one of the major scientific barriers is the lack of clinical trials directly evaluating regenerative therapies—especially mesenchymal stem cells (MSCs)—for chronic urticaria. Most MSC studies focus on asthma, autoimmune diseases, or chronic wounds, leaving allergic dermatoses like urticaria underexplored (Macloughlin, 2022). Furthermore, there is no published research focusing specifically on healthcare workers (HCWs) or occupational urticaria, creating a substantial gap in evidence. As a result, clinicians must rely on extrapolated data from non-allergic conditions when considering regenerative options for CU. Without direct trials, it remains difficult to evaluate dosing, delivery method, or durability of MSC-based interventions in allergic diseases. This limits translational progress and regulatory approval, which typically require condition-specific clinical validation. Bridging this evidence gap is essential for establishing regenerative medicine as a viable option for urticaria.

In addition to scientific limitations, practical implementation challenges hinder the adoption of regenerative therapies in allergic skin diseases. MSC-based products—especially autologous or engineered cell therapies—are expensive and resource-intensive to manufacture, store, and administer (Huang et al., 2020). Access is further complicated by specialized handling requirements and variable regulatory approvals across regions. Even if therapies prove safe and effective, long-term immunologic monitoring is necessary to evaluate outcomes such as recurrence, hypersensitivity, or loss of efficacy. Furthermore, cell heterogeneity, batch variability, and lack of quality control standards present manufacturing and scalability challenges. These logistical issues make it difficult for smaller healthcare systems or occupational clinics to implement regenerative approaches. Therefore, simplifying delivery platforms—e.g., secretome- or exosome-based products—could help bypass many of these practical hurdles.

Despite these barriers, opportunities exist to design trials specifically targeting chronic allergic skin conditions like CU. Omalizumab has shown strong evidence of efficacy in chronic spontaneous urticaria, with multiple trials demonstrating improvement in symptoms, quality of life, and sustained control (Jia & He, 2020); (Rubini et al., 2019). However, the combination of omalizumab with MSCs or MSC-derived products has not been studied, despite theoretical synergy. MSCs modulate mast cell activation and cytokine imbalance, while omalizumab neutralizes circulating IgE, suggesting a dual-acting therapeutic potential. Trials integrating regenerative and biologic therapies could yield superior control over refractory or occupationally induced urticaria. Moreover, studying HCWs with documented latex hypersensitivity may allow for stratified analysis of treatment efficacy across exposure levels. This would enable the development of more personalized and effective care strategies in occupational medicine.

Finally, robust safety and immunologic profiling remain essential components of future regenerative trials. Although MSCs are generally considered safe, their immunomodulatory nature raises concerns about long-term immune suppression or unanticipated interactions with allergens. Trials in other fields (e.g., veterinary and renal applications) suggest high tolerability, but allergy-specific data are still scarce (Jeung et al., 2024). Immunologic assays evaluating mast cell activity, histamine levels, and cytokine profiles pre- and post-treatment will be key to evaluating efficacy and risk. Furthermore, follow-up protocols should monitor relapse rates, recurrence under allergen re-exposure, and systemic immune alterations. Without these safety data, the widespread use of MSCs or PRP-based therapies in urticaria—especially for vulnerable populations like HCWs—remains premature. Thus, well-designed, longitudinal studies are a critical next step in advancing the field.

Future Directions

Future research should prioritize early-phase clinical trials evaluating the safety and efficacy of MSCs, secretome-based products, or PRP in treating chronic urticaria and allergic dermatoses. Innovative formulations that integrate PRP, hydrogels, and MSC secretome may provide localized,

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long-lasting immune modulation in the skin. In occupational settings, there is a growing need for personalized regenerative strategies tailored to sensitized healthcare workers. Such approaches could support symptom control without requiring full allergen avoidance. Long-term goals should include reducing sick leave, enhancing return-to-work outcomes, and improving overall quality of life for affected workers. Cross-disciplinary trial designs and outcome tracking in real-world work environments will be key to advancing clinical adoption.

CONCLUSION

Stem cell-based immunomodulatory therapies hold promise for mitigating inflammation and promoting tissue repair in latex-induced chronic urticaria among healthcare workers. By targeting key immunopathological mechanisms such as mast cell activation, histamine release, and Th2 cytokine imbalance, regenerative approaches using mesenchymal stem cells (MSCs), secretomes, and platelet-rich plasma (PRP) offer a novel pathway to restore skin integrity and immune homeostasis. However, the translational application of these therapies remains limited by small-scale studies, lack of standardized protocols, and insufficient clinical validation. Future research should focus on optimizing delivery methods, defining long-term safety profiles, and conducting controlled clinical trials in occupational cohorts to establish efficacy and feasibility in real-world healthcare settings.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article. All authors have approved the final version of the manuscript and confirm that there are no financial, personal, or professional affiliations that could be perceived as influencing the findings or interpretation of this study.

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